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THE DIAGNOSIS AND GENERAL TREATMENT OF SYPHILIS.

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It cannot be emphasized too frequently nor too emphatically that the fate of the syphilitic individual depends largely upon the early diagnosis of his infection and the intensity with which his treatment is carried out in the first six months. It is in the accomplishment of this purpose that the modern aids to diagnosis have rendered such invaluable service. Unfortunately, this is not universally recognized, for clinicians are still met with who decry these modern precision methods, claiming that the trained observer can recognize with his eye and sense of touch all that can be revealed by laboratory procedures. The fallacy of this claim is demonstrated from time to time by patients who come with the following history: Fifteen to twenty years ago they consulted the best-known syphilographer at that time, who made a diagnosis of chancroid, telling the patient that his future, as far as the present infection was concerned, was secure and that he had nothing to fear. Reassured by such information no treatment was taken, and years after these patients consult for involvement of the central nervous system, an interstitial glossitis, an aortitis, or other late manifestation of the disease. It is now well known that the soft sore frequently harbors the parasite of syphilis, and owing to the longer incubation

period of the latter, does not develop its characteristic features until after the expiration of two or three weeks, or they may be entirely absent. It seems superfluous, therefore, to insist that the secretion of all venereal sores be searched for the Treponema pallidum. Failing to find it, one should not give a favorable prognosis until repeated examinations have been made, including the Wassermann reaction. With proper training the dark-field illumination is simple of application and the spirochete of syphilis readily differentiated from other types. Microscopic corroboration of a suggestive sore is absolutely essential in many cases, owing to the protean appearance chancres may assume. While, to the skilled eye and finger, a Hunterian chancre with indurated edges needs no confirmation, the pathognomonic features may be lacking altogether, or a papule or herpetic lesion may represent the only local reaction called forth by the treponema. In urethral sores and suspicious extragenital lesions the correct and early diagnosis is of great importance, and their nature finds a ready means of differentiation in the dark field. The value of the latter is further appreciated in developing chancres before the clinical characteristics suggestive of the infection appear. Recently, I had the opportunity to examine an initial lesion which had made its appearance only on that day. It was situated on the left side of the foreskin, was about the size of a pinhead, capped by a tiny crust. The patient had been exposed three weeks before. There was no lymph-node enlargement and the Wassermann reaction was negative. The advantage of early treatment in such cases and consequently the more favorable prognosis are too obvious for discussion. Success in demonstrating the organism depends largely on the care taken in obtaining serum for examination. This should be secured from the depths of the lesion. Antiseptic washes, ointments, or other applications frequently interfere with the demonstration, and in cases of doubt the examination should be repeated on successive days, the lesion being kept clean meanwhile with saline solution.

The time of the appearance of the Wassermann reaction cannot be estimated with mathematical exactness, as it is dependent upon the rapidity with which the organisms gain the general circulation and the reaction provoked by them. This we know varies in different individuals. In some cases the reaction is positive in the fourth or fifth week after exposure; in others not until the seventh or eighth week. A negative reaction does not necessarily mean that generalization of the spirochetes has not taken place. Uhlenhuth and Mulzer[1] obtained positive results in animal inoculations with the blood of primary syphilitics in whom the Wassermann reaction was still negative. With the development of the rash it is usually definitely established. I have in a very long series of untreated

[1] Berl. klin. Wchnschr., 1913, p. 769.

cases found only one with a fresh maculopapular eruption in which the Wassermann was only weakly positive. If treatment is carried out on a definite and intensive plan in the primary stage a negative reaction will remain continuously negative, or in the event of its being already positive it shows itself susceptible of reversion more readily than when the infection is of several years' duration. Too much stress cannot be laid on the fact that the amount of treatment is individual; this must be kept in view in every case under consideration. There are patients treated under the old régime with mercury by mouth, inunctions or injections, or these methods combined, who now have a negative blood reaction, exhibit no symptoms referable to the nervous or circulatory system, and are negative after a provocative injection of salvarsan. Others treated five years ago with a minimum amount of salvarsan (*i. e.*, one or two injections) and mercury may likewise be considered cured according to our present-day criteria. On the other hand, there are a certain number of patients in whom multiple courses of salvarsan and mercury are necessary to bring about and maintain negative findings. In some cases we will even fail to convert a positive into a negative reaction without endangering the health of the patient. A resistant serum cannot always be accounted for on a clinical basis, for often, as far as we are able to ascertain, nothing can be demonstrated to explain its persistence. In by far the vast majority, however, involvement of the cardiovascular or nervous system will furnish an explanation.

The interpretation of the Wassermann reaction is as important as that of the clinical phenomena of the disease, but the burden of proof should not rest with its presence or absence alone. In ocular syphilis, disease of the vascular apparatus, obscure visceral or nervous involvement and in latent syphilis of hereditary origin positive manifestations may be present and the Wassermann reaction negative. To make some of these points clear the following cases are quoted:

Case I.—Man, with active secondary skin and throat lesions at end of October, 1914. On October 31, November 8 and 20, and December 13 respectively, 0.6 gm. salvarsan. January 8, 1915, perivasculitis. Wassermann said to have been negative. Under rubbings and calomel, eye lesions cleared. Discontinuance of treatment was followed by relapse from a new focus. March 31: Spinal fluid, ——; serum, ——. Under injections of a soluble salt and potassium iodide the eyesight again improved. Treatment interrupted in September. Wassermann, December 29, 1915, March 16, 1916, + + + +.

Case II.—Man, aged fifty-seven years, with cerebral endarteritis and capillary fibrosis at the maculæ. Infection over thirty years ago. Recurring ulcerative skin lesions; scaling eruption palms; mental depression, vertigo, loss of memory; inability to concentrate on work;

failure of sexual power. He recalls severe headaches, leg pains, and mental excitability in secondary period twenty-nine years ago. Eye reflexes, knee-jerks, and ankle-jerks present without noticeable abnormality. Treatment during many years with mercury and potassium iodide. Repeated negative Wassermann reactions during 1911 and 1912. In 1913, after treatment with potassium iodide and mercury, Wassermann became + + + +, and after further treatment ——. Spinal fluid March 31, 1915: cells, 0; globulin, + +; Wassermann, ——; gold test, ——; blood Wassermann, + + + +. Treatment continued during 1915 was followed by improvement in all respects. Vertigo and depression disappeared; capacity for work increased. He was less excitable and memory and sexual power returned. Evidence of vascular disease in eye also disappeared.

The noteworthy features in this case are the long persistence of a negative Wassermann reaction, with scaling palms analogous to leukoplakia, the obscure character of the nervous symptoms, evidence of vascular disease in eyes, result of fluid examination pointing to cerebral endarteritis, Wassermann reaction becoming positive after treatment by iodides and mercury, and relief of all symptoms by persistent treatment.

Case III.—Girl, aged twenty-one years; hereditary syphilis. Scars of an old interstitial keratitis. For five years had suffered from migraine type of headache. Serum ——; spinal fluid ——. After three injections of salvarsan serum became strongly positive.

Case IV.—Man, aged forty-nine years; chancre when sixteen years old, followed by secondaries. For three years internal treatment; no relapses. In the summer of 1915 he complained of increasing fatigue and soreness over the right apex. Repeated examinations for tubercle bacilli negative. Von Pirquet, +; Wassermann,——. From roentgen-ray and physical examination, diagnosis of syphilis of the bronchial glands was made. Wassermann, January 7, 1916, ——; January 11, 1916,——; mixed treatment for one week evoked a + + + + reaction.

The above abstracts show that not rarely it requires not a single but several injections of salvarsan or the prolonged use of mercury and potassium iodide before a provocative reaction is obtained.

The Wassermann test is of great value in the recognition of syphilis as a causative factor in conditions of obscure etiology in children. Also in anticipating future development, as in many cases of congenital syphilis no sign or symptom is present excepting a positive blood reaction. The children are normal mentally and physically, and excepting the positive serum and a history of syphilis in the father there is nothing suggestive of a luetic taint.

The tendency of the present day is to deny categorically the paternal origin of syphilis, admitting only the possibility of transmission from the maternal side. While this would simplify the

problem it offers no solution for the cases in which the mothers remain symptom-free and Wassermann-negative; some patients observed after thirty years who have had one or more children clinically and serologically syphilitic. Do such women have a modified form which disappears spontaneously or do they escape the infection altogether?

The only criterion of cure in a man contemplating matrimony is a negative Wassermann which has persisted for at least a year after intensive treatment and which remains negative after a provocative salvarsan. The element of time while of importance in modifying the infection is of vastly less value than the revelation of the serological test. In a family seen by me a short time ago the father was infected in 1901, for which he had inunctions and potassium iodide each year for six years. He was married in 1907. The first child was born in 1908, was well nourished and healthy until August, 1915, when he developed partial deafness of the right ear. His spinal fluid showed: cells, 20; globulin, + +; Wassermann, ——; serum, + + +. The second child was born in 1913, is splendidly developed in every way, and has never shown any symptoms but has a + + + + Wassermann. The mother's reaction is negative; she has never given any evidence of the infection, has had no miscarriages and no treatment. The father's reaction is + + + +.

The diagnostic import of the spinal-fluid examination grows more and more apparent with time. The cell count, Wassermann reaction, globulin and colloidal gold tests enable us not only to determine the activity of a syphilitic process in the brain or cord but serve to distinguish the various pathological types of syphilis affecting the cerebrospinal system and in many cases to differentiate between these and non-luetic affections. A case in point is the simulation of the multiple neuritis of diabetes by the tabetic syndrome.

A patient, aged thirty-seven years, was referred to me with the diagnosis of tabes. He had had a chancre twelve years before, followed by secondaries and treatment for three years. For four weeks he had had pain and numbness in his fingers and feet, with an insecure feeling in the soles of his feet, difficulty in walking and unsteadiness. For six or seven years he had had periodic attacks of gastric distress, with dizziness and extensive areas of hyperesthesia; sexual paresis had been present for one year; eyes were normal; patella and Achilles reflexes absent. Laboratory examination showed: blood Wassermann, ——; spinal fluid; cells, 8; globulin, ——; Wassermann, ——. His urine contained a large amount of sugar. Diagnosis: diabetic polyneuritis.

Another case was sent with the diagnosis of taboparesis. The patient gave a history of syphilis twenty-five years previously, with repeated courses of treatment. His pupils were irregular and fixed to light, knee-jerks absent and lightning pains in the lower extremi-

ties. It was claimed that he had shown evidence of mental deterioration as manifested by irascibility, loss of memory, etc. The patient had been an alcoholic for over thirty years, having taken six to eight drinks daily, with occasional intermissions. His blood and fluid examinations were absolutely negative. In this case a correct diagnosis might have been made by a skilled diagnostician, but to the average practitioner the picture presented was that of tabes or taboparesis. From the laboratory stand-point there are two possible conclusions: either the spinal-fluid findings were rendered negative by the treatment received or the entire syndrome was due to alcoholism and the question of syphilis as an etiological factor left in doubt. The latter supposition is the more probable, experience having shown that in paresis, negative findings throughout are not brought about by the amount of treatment the patient has had.

With faulty diagnoses like the above on the negative side of syphilis, those on the positive side merit citation, for not infrequently patients with obscure pains, febrile attacks, gastric and rectal crises, irritability, failure of memory, etc., give a history of having long been treated for neuresthenia, rheumatism, neuritis, and various other indefinite conditions. Such patients sometimes admit having had a specific infection with indifferent treatment; others disclaim all such knowledge.

One of my clinic patients, a young woman, aged twenty-four years, had within the past two years about twenty attacks of gastric crises. She was usually removed to a hospital, and on two occasions was operated upon, once for appendicitis and again for gall-stones. She has been married five years and has had several miscarriages. The only objective manifestation of tabes was slightly sluggish pupils. Her serum was strongly positive, her spinal fluid showed 45 cells, + + globulin, Wassermann + + + + to 0.6; colloidal gold, luetic curve.

Rectal crises are less commonly seen and their nature often fails of recognition. A patient under my care was treated nineteen years ago for primary and secondary syphilis. For the past two years he had had attacks of severe pain in the rectum, for which an operation had been advised. His pupils were unequal and sluggish to light, knee-jerks normal, station good, bladder slow, sexual power weak. Blood, + + + +; spinal fluid; cells, 150; globulin, + +; Wassermann, + + + + to 0.4; colloidal gold, luetic curve. His pains were markedly aggravated by the first few intraspinal treatments.

The so-called lightning pains in tabetics are often treated symptomatically or disregarded entirely.

A patient, aged thirty-four years, infected ten years ago, had suffered from pains in his legs for seven years. His spinal fluid showed: cells, 42; globulin, + +; Wassermann, + + + + to 0.2; colloidal gold test, luetic curve; serum + + + +.

Another patient, aged thirty-nine years, infected seven years ago, complained chiefly of stabbing pains in various parts of the body which began four years ago in the lower extremities. His pupils were irregular and sluggish to light, his knee-jerks weak, ankle-jerks absent. Spinal fluid: cells, 8; globulin, + +; Wassermann, + + + + to 0.2; colloidal gold test, luetic curve; serum + + + +.

The premonitory symptoms of developing paresis are also frequently overlooked. This is illustrated by the following case:

Man, aged forty-two years, infection in 1905, for which he was treated for seven years with mercury internally and by injection. He had had no symptoms since 1912. In June, 1915, he had a convulsion, unconsciousness lasting one-half hour. The attack was attributed to colitis and intestinal absorption and treatment directed against this until December, 1915, when he had a second convulsion. His spinal fluid showed: cells, 45; globulin, + + +; Wassermann, + + + + to 0.1; colloidal gold test, paretic curve; serum, + + + +.

In the light of more recent investigations an analysis of the spinal fluid is not complete unless the gold sol test is performed in addition to the Wassermann reaction and cytological and chemical examination. The theory of this reaction is based upon the observation made by Zsigmondy in his original work on metallic colloidal solutions in 1901, that solutions of electrolytes precipitate colloidal gold; that in the absence of an electrolyte, proteins will also cause such a precipitation, while in the presence of an electrolyte they inhibit precipitation. These principles were applied by Lange[2] in 1912 to the examination of the spinal fluid. He found that by a modification of the Zsigmondy technic, normal and pathological fluids could be differentiated from each other as well as syphilitic from other affections of the central nervous system. While the test has been employed by a number of workers during the past few years in the diagnosis of syphilis, it has not had the general application it deserves owing to the difficulty of making the solution. This phase happily is now in large measure overcome by the admirable work of Dr. Miller[3] and his associates. Through their investigations every detail in connection with the technic of its preparation has been so carefully developed that the standardization of the reagent is now possible, and consequently more uniform results in the reaction.

Just how the reaction occurs and the nature of the protein or proteins involved is not known. Views advanced are that it is due to the presence of abnormal albumin or possibly the presence of an excessive amount of the normal. It was originally found that the colloidal gold was a qualitative determination which, according to

[2] Ztschr. f. Chemotherapie, Orig., i, 1912, p. 44.
[3] Bull. Johns Hopkins Hosp., xxvi, 1915, p. 391.

dilution, gave different reactions. Lange, therefore, sought the explanation in a different qualitative mixture of proteins while Zalozieki interpreted it as an immunity reaction, and Jaeger and Goldstein as a physical phenomenon of an electrical nature. Miller, Brush, Hammers, and Felton have shown that the substance is dialyzable. The amount of albumin normally present in the spinal fluid gives no reaction and a change in reaction is therefore indicative of some abnormality as to quantity or quality.

The test itself, very easily and quickly made, consists of a series of color changes which occur so characteristically and constantly that they may be said to be specific. It is performed with ten dilutions of spinal fluid in geometrical progression from 1 to 10 to 1 to 5120. The color change depends on the amount of colloidal gold precipitated and varies from the negative salmon red through red blue, lilac or blue, blue gray or gray, and colorless. These changes may be plotted in curves or are arbitrarily expressed from zero to five. A negative colloidal gold would show no change and would therefore be expressed as 0000000000. In tabes and cerebrospinal syphilis the reaction occurs in the lower dilutions with the intensity of the change in the third and fourth or fourth and fifth tubes. The term "luetic zone" or "luetic curve" is used to describe this reaction. The reading would be as follows: 1133200000 or 1223320000. In meningitis of non-syphilitic origin the maximum change occurs beyond the syphilitic zone—that is, in the higher dilutions—while in paresis precipitation of the colloidal gold occurs regularly in the first four to eight tubes with decolorization or a turbidity, and the reading represented as 5555431000 or as many fives as there are decolorized tubes. To this zonal change Miller and Levy applied the term "paretic curve." A properly standardized—that is, a neutral solution of colloidal gold—shows either no change at all with a normal spinal fluid or produces a slight variation with a bluish nuance in the first four or five tubes which is negligible. Some cases may even give a change to a frank red blue in the first four tubes, so that the reading would be 1111000000, but with all the other laboratory findings negative it has been shown this had no diagnostic import.

It may be said that, as a rule, there is a parallelism between the other positive findings in the fluid and a positive gold reaction. The significance of any one of the individual abnormalities must be appreciated before a proper interpretation can be placed upon the laboratory findings. We know that a lymphocytosis alone is not pathognomonic of syphilis as a mild grade is met with in other affections of the central nervous system and that the cell count cannot be relied upon to differentiate between tabes, cerebrospinal syphilis, and general paresis, as an equally high pleocytosis may be met with in any of these conditions. So too the presence of globulin alone indicates organic disease of the brain or cord, but

does not separate syphilitic from non-syphilitic disease. More positive information is derived from the complement-fixation test, as a positive Wassermann occurs only in lues. However, this test by itself does not supply a differential diagnosis as fixation to 0.2 c.c. or lower is met with not only in paresis but in some cases of progressive tabes and cerebrospinal syphilis. On the other hand, with a distinctly syphilitic process, as in cerebral endarteritis, abortive or stationary forms of tabes, and some types of cerebrospinal syphilis, the Wassermann may be completely negative. In the last-named cases a supplementary gold test is of value in demonstrating the luetic nature of the condition. Its greatest value and by far most prominent rôle, however, is in distinguishing between paresis and the conditions which simulate it as well as its prognostic significance in tabetics who show no mental impairment but give a paretic curve. Since the application of the gold sol test in my laboratory a number of patients in whom no cerebral involvement was suspected have given the curve characteristic of paresis. The following cases may be cited as illustrations:

Mr. X., aged thirty-nine years; infection thirteen years ago; secondaries denied. Mercury internally for one and a half years. In 1914 he developed pain in the legs, arms, and neck. When seen by me in March, 1915, his pupils were fixed to light and accommodation; knee-jerks and Achilles-jerks were absent: Romberg was present; slight bladder incontinence; sexual power weak. Spinal fluid examination: cells, 75; globulin, + +; Wassermann, + + + + to 0.4; colloidal gold, decolorization in first five tubes (5555543200). His family had observed no mental trouble, although they thought he had been more irritable and less dependable in business transactions during the preceding year. He has been under active intraspinal treatment; the curve and Wassermann remain unchanged; clinically there has been no change in his condition.

Mr. Y., aged thirty-nine years; infection in 1897. In 1906 had double vision and bladder weakness. In 1912 had tingling in feet, unsteadiness in gait, and great fatigue. He has absent knee-jerks and a Charcot joint of the right hip. The latter part of 1914, according to his family, he was depressed and very forgetful. A spinal-fluid examination made after he had had intensive intravenous and mercurial treatment showed: cells, 2; globulin, + +; Wassermann, + + + + to 0.6. A gold sol test made in May, 1915, read 5555432200.

Mr. Z., aged twenty-seven years. Chancre eight years ago followed by secondaries of the skin and mouth. Treatment internally until 1910, when he developed paralysis of the left external rectus. December 20, 1912, station and gait normal; knee- and ankle-jerks hyperactive; coördination perfect; no sensory changes; objectively viscera normal; pupils normal. Complains of shooting pains in legs, tingling and cramps in calves. Blood Wassermann ——.

Spinal-fluid examination in December, 1913: cells, 26; globulin, +; Wassermann, + + + + to 0.4. Colloidal gold test made in May, 1915, and all subsequent ones give a paretic curve. This patient has had, since the latter part of 1913, 30 intravenous injections of salvarsan and 30 intraspinal injections in addition to mercury. His present fluid examination shows: cells, 3; globulin, + + +; Wassermann, + + + + to 0.4. He is of powerful physique, and during the time he has been under treatment has interrupted his work, which is that of a stationary engineer, only for intraspinal therapy. No change in character or personality has been noted.

In analyzing those cases of general paresis which I have had under my care from time to time the striking feature has been the multiform clinical picture, and in many the absence of the chief symptoms of the affection, namely, the typical cerebral disorders, as writing and speech defects, tremor and memory defects. Some of the patients have had simply a convulsion or two or fainting attacks, while a few others have exhibited no signs referable to the condition, the diagnosis being based mainly on the persistent positive Wassermann reaction and the gold sol test. While it would be premature to make a definite pronouncement as to the prognostic significance of the paretic curve, we must bear in mind the teaching of postmortem findings that anatomical changes in general paresis may long antedate the clinical manifestation. In patients, therefore, who are under continuous observation, and especially those who are receiving intraspinal treatment when the fluid can be examined at regular intervals, the presence or the development of the paretic curve should excite a strong suspicion that these patients may later develop the clinical syndrome. My procedure with these patients is to advise the family or business associates of the possibilities in the case, especially when large business interests are involved, and to treat these cases intensively with the hope that we may anticipate perhaps, retard or arrest, the degenerative cerebral changes. In the type where the meningovascular changes are preponderant, as evidenced by a high cell count, the prognosis is more favorable than where the parenchyma is chiefly involved.

The colloidal gold test has been uniformly positive in all cases with the clinical earmarks of general paresis. In several cases under intensive treatment the paretic curve has changed to the luetic curve. In early syphilis of the central nervous system, *i. e.*, in the early secondary period, I have in several instances found the luetic curve with a negative Wassermann, the only other abnormalities being a slight increase in globulin and lymphocytes. Clinically, these cases gave objective evidence of implication of the central nervous system.

In estimating the number of individuals with abnormal spinal fluids in the secondary stage of the infection I have frequently expressed the conviction that no larger percentage showed definite

changes than later developed frank symptoms referable to the neural axis. Further experience strengthens this conviction. In a series of cases examined two years ago abnormalities were demonstrated in less than 20 per cent. In a series of 63 cases recently punctured 10 showed very slight changes as to lymphocytosis and globulin content, coming well within the border-line cases, while 15 exhibited a definite increase in cells and globulin with a positive Wassermann in 7. The cases were all within the first year of infection, untreated or practically so. The standard used was a cell count over 5, a globulin content demonstrated by the Pandy test, a positive Wassermann with 2 c.c. or less of fluid and the color changes elicited by the Lange test. Statistics in the literature treating of abnormal fluids in the secondary stage of lues are variously quoted at from 10 per cent. to 90 per cent. In attempting to reconcile such an apparent disparity it is possible that too much significance has been attached to minor changes, as increased pressure, increase of a few cells, or a trace of globulin. These are probably only transient conditions and part of the systemic infection. My belief is that only such individuals who show very conspicuous changes, as evidenced by a definite cell count, globulin, and positive Wassermann, are candidates for one or the other of the different clinical types of cerebrospinal syphilis. Whether we invoke special conditions as a particular strain or individual predisposition as necessary corollaries to infection of the central nervous system the deduction is forced upon us that in a large majority of patients the organisms must be destroyed spontaneously or by therapeutic agents administered in the ordinary way. The proportion of syphilitics who develop disease of the nervous system is given at from 9 per cent. to 25 per cent. These figures it must be borne in mind were compiled before the era of laboratory diagnoses and their accuracy cannot pass unchallenged.

Treatment. In discussing the treatment of syphilis there are certain general considerations in regard to the therapeutic armamentarium worthy of mention. The object of any energetic antiluetic treatment is the destruction of the greatest number of spirochetes in the shortest possible time. From our knowledge of the immunological and pathological processes in the disease this is best accomplished in the early stage, and from experience accrued during the past five years is more readily and more certainly brought about by the combination of salvarsan and mercury. It has been amply demonstrated that salvarsan is essentially a spirocheticide which, while it has very little influence on the organisms in the test tube, is actively germicidal *in vivo*. Mercury is the best-known germicide *in vitro*. When employed experimentally in animals infected with trypanosomiasis or relapsing fever it is practically inert as far as its effect upon the organisms is concerned and the fatal termination of these diseases is not delayed. In spite of this negative evidence,

however, it has been demonstrated empirically for many years that mercury has a curative effect in syphilis, and since the cure depends upon the more or less complete saturation of the patient with the drug its action is presumably a direct one. Nor has it been shown that the iodides are spirochetotropic in their action. Potassium iodide has no effect on the early lesions of syphilis and only a neglible one in rendering the Wassermann reaction negative. It has, however, a profound physiological effect aside from its specific therapeutic action. The latter, in gummata, has been explained by Jobling[4] as due to the neutralization of the antiferments which prevent autolysis and absorption of the necrotic tissue, at the same time rendering the infecting organisms which had previously been protected by the necrotic tissue accessible to the parasiticide.

Salvarsan, by virtue of its spirocheticidal properties, finds its greatest field of usefulness in primary and secondary syphilis when the organisms are abundant. In the later stages, when they are few in number and the tissue changes are more marked, one would naturally expect less results from this agent. As a matter of fact, in gummatous and periosteal lesions and all the active manifestations of late syphilis the therapeutic effect of the drug is almost as intense as in the early contagious period. This is especially true of patients who have been treated over a long period of years with mercury and potassium iodide and have become more or less immunized to the action of these drugs. I have seen patients with periosteal lesions and febrile attacks and numerous cases of so-called malignant syphilis in whom mercury and potassium iodide were practically inert very quickly respond to salvarsan. The following case is a typical example:

Woman, aged forty-two years; infection eleven years ago. Treatment for three years by mouth and injections. When seen September 7, 1915, she was suffering from periostitis of the right parietal and frontal bones, of the sternum and right shoulder. For several months she had been running an evening temperature of 101° to 101.5° F., with headache. During this time mercury and potassium iodide were administered without effect. On September 9, 1915, she was given 0.25 gm. salvarsan. Her pains, headache, and fever disappeared in two days, and there was a most marked general improvement. Since that time she has had six small doses of salvarsan and two of neosalvarsan, and has gained over thirty pounds in weight.

While it is possible, theoretically, to formulate a method of treatment in the various stages of syphilis, as a matter of practice the best devised plan must preëminently be an elastic one, subject to the modifications called for by the susceptibility of the patient to the drugs and to intercurrent reactions which take place from time to time.

[4] Arch. Int. Med., xv, 1915, p. 286.

In early active syphilis, salvarsan alone has been followed by neurorecurrences and monorecurrences or early tertiary lesions. In cases of initial lesion seen before the Wassermann reaction is positive salvarsan may perhaps be given without such danger. It is better, however, not to rely on this drug alone to establish a complete cure but to give the combined treatment. It has been claimed by Wechselman that such combination was more apt to produce kidney involvement, but this contention has not been substantiated by the majority of observers. My own plan is to give a course of mercury with the salvarsan, the number and size of doses of both agents depending upon sex, body weight, and general condition of the patient.

The salvarsan is given in courses of five or six injections in doses of 0.3 gm. to 0.5 gm. for men and 0.25 to 0.4 gm. for women at intervals of one week to ten days. The mercurial injections are given every day or every alternate day if a soluble salt is employed, or once a week if an insoluble one. My preference in case of the former is the bichloride of mercury in courses of twenty to thirty injections given daily or every other day. Of the insoluble preparations, gray oil, (in the form of mercurial cream), of which 5 minims represent one grain, in series of ten to twelve injections, or salicylate of mercury (40 per cent. suspension) in dosage of 1 to 3 grains gradually increased, ten to twelve injections constituting a course. Both salvarsan and mercurial courses are followed by a rest period of six weeks and then the procedure is repeated. Wassermann tests are made periodically, but treatment is not interrupted because of a negative reaction until the adequate amount of medication has been given.

When visceral lesions are present salvarsan should be used in small doses repeated at intervals determined by each case. In cardiac conditions it is better to precede with mercury or mercury and potassium iodide. They are greatly benefited by the latter drug. I have given salvarsan in these cases without untoward symptoms. Whatever form of treatment is decided upon it is important to carry it out persistently. The progress of any active condition can be checked, but anatomical changes like sclerosis or aneurysm are of course permanent.

In primary syphilis before the Wassermann has become positive it is possible to abort the infection both clinically and serologically. While in the past this has been accomplished in some cases with a minimum amount of treatment, such patients now receive two courses each of salvarsan and mercurial injections.

In secondary syphilis with a positive Wassermann it is frequently necessary to give three courses of salvarsan with mercury before the desired effect on the serum reaction is obtained.

In tertiary syphilis the method of treatment depends upon the tissues or organs involved. It is of advantage to combine the courses of salvarsan with intramuscular injections of mercury and

to follow this with the prolonged use of potassium iodide and mercury in the form of mixed treatment.

In so-called latent syphilis the administration of salvarsan alone often fails. I have a number of cases in whom the Wassermann reaction continued to show complete inhibition after repeated courses. In many individuals with a positive serum when the nervous system is not involved, careful examination may reveal an aortitis, interstitial glossitis, or the remains of a hepatitis or other viscereal lesion with residua sufficient to call forth a Wassermann reaction. It often requires the most painstaking care to reveal the possible location of the disease. For instance, the nervous system may be implicated and only manifested by slight pupillary irregularity or a slight change in the knee-jerks which might easily be overlooked unless the examination is made by a carefully trained clinician. The spinal fluid should be examined when these deviations are indicative of involvement of the cerebrospinal system, and in all cases with a persistent blood reaction when a focus cannot be determined in the skin, mucous membranes, or viscera. Even in the absence of signs pointing to such implication a Wassermann which does not respond to therapy is an indication for lumbar puncture. More benefit is derived in latent lues from the old-fashioned mixed treatment—that is, a combination of mercury and potassium iodide in a liquid menstruum—than from salvarsan alone or combined simply with potassium iodide. With mixed treatment I have in many instances accomplished the reversal of the Wassermann which had remained persistently positive under salvarsan and mercury.

From Stühmer's[5] experiments the greater part of salvarsan introduced intravenously is stored in the lungs, liver, and spleen in about equal quantities. These form depots from which the drug reaches the circulation, most of it probably passing unchanged through the kidneys and intestines. From the latter a sufficiently large amount is excreted, so that if intestinal disturbance is present marked toxic oxidation products are produced which, when absorbed, may lead to severe reactions.

The reaction following the use of salvarsan may be divided into immediate and delayed.

1. *Immediate.* The commonest symptoms are flushing of the face, cyanosis, a sense of fulness in the head, and precordial distress with slight dyspnea. They usually come on during the administration and may be regarded as anaphylactoid in character. They last but a few minutes and many patients complain of feeling weak or enervated for the next day or two. More rarely patients are met with in whom vomiting occurs during the administration. In a case under treatment this takes place after 15 or 20 c.c. of the solution are introduced. When the attack has passed off the remainder of the

[5] Arch. f. Derm. u. Syph., cxx, 1914, p. 589.

dose is taken without trouble. A psychical element is probably present in this case. Occasionally attacks of severe pain in the lumbar region come on during the flow of the drug and necessitate its interruption. After half an hour or so it passes off, the patient experiences no further inconvenience, or he may after an hour or more have a chill with temperature and vomiting. These reactions usually come on after several injections have been given.

2. *Delayed.* The symptoms appear after twenty-four hours, three days, or longer. Those after twenty-four hours are usually gastro-intestinal, preceded by a chill or chilly sensation, and are characterized by vomiting and diarrhea with a temperature. In another type there is simply malaise for a few days and then the patients become actively ill with vomiting, fever, and a rash or jaundice, the latter the result in all probability of the action of the arsenic on the liver cells. Rarely suppression of the urine is encountered, and this may be attributable to the direct action of the drug on the renal vessels.

As the majority of the reactions come on only after several doses have been given, one should be warned by their occurrence and regulate the interval and dosage accordingly. In cases in which a dermatitis has been present the drug should not be repeated within six months or a year. I have seen death follow in a patient in whom the significance of such a rash was disregarded during intensive treatment with neosalvarsan. The injections were continued and a most extensive exfoliative dermatitis developed, ending fatally. In my own experience there have been two deaths which may be said to have been directly attributable to salvarsan. In the first, a man, aged forty-two years, the infection was nine years old. For this he had had treatment at intervals for six years. When seen he presented a tubercular ulcerating syphilide of the face, scalp, and left arm. He was given mixed treatment, under which the eruption disappeared. On December 30, 1914, he received 0.35 gm. salvarsan, January 11, 1915, 0.4 gm., January 22, 0.4 gm. After the last treatment he had a slight reaction and a change was made to neosalvarsan, 0.6 gm., on February 10, 1915, which was repeated February 20, 1915. Three days later he developed a temperature of 102° to 104° F., and a generalized dermatitis which partially subsided after a week and then recurred with increased intensity. It involved the entire cutaneous surface, the integument became thickened, leathery-like in consistency, and pigmented. After a few days abscesses developed in various parts of the skin followed by a recurrence in temperature and rapid heart action. These abscesses were opened and drained, but in spite of all the care which could be given the patient death ensued. In this case death could be primarily ascribed to the salvarsan dermatitis and secondarily to the sepsis which followed the cutaneous involvement. The urine showed on March 13 a marked trace of albumin with a few blood and pus cells and a few epithelial casts. On the twenty-third

only a trace with a few hyalin casts. It should be added that the patient was markedly alcoholic.

In the second case a woman at the City Hospital, treated in 1911 for an early malignant infection, after the second dose developed suppression of the urine, marked reduction of the blood pressure, vomiting and collapse within twenty-four hours after administration. Autopsy made by Dr. Larkin revealed degenerative changes in the kidney epithelium, in the suprarenal bodies and fatty degeneration of the liver cells.

As mercury has a great affinity for the renal cells the kidney is one of the prime organs to suffer in mercurial intoxication. Hence it is important in the administration of the drug to determine the renal eliminating function and to examine the urine from time to time. From their studies of the various preparations of mercury Schamberg, Kolmer, and Raiziss[6] concluded that the toxicity of the different salts is proportional to the amount of pure mercury contained. After absorption the drug circulates about as a compound of mercury albuminate and sodium chloride, excretion taking place chiefly in the feces and only to a small extent in the urine. It is believed that a definite ratio is maintained between the amount excreted by the kidneys and that present in the general circulation and passing through the renal vessels. The rapidity with which it appears in the urine is taken as an indication of the rapidity and intensity of its effects in the body, its elimination corresponding with its cessation of activity. Its excretion continues for months, and it may appear again after the urine has become free, from which it is deduced that mercury is stored up in the different organs and unless elimination keeps pace with absorption poisoning will result.[7]

When inunctions are employed mercury appears in the urine from the first day on. Elimination gradually increases to a certain point, then remains for weeks nearly constant, and after cessation of treatment falls again gradually.[8] The method is very efficacious, but, unless in the hands of a professional rubber, uncertain. Its disadvantages are constant supervision and filthiness.

When given orally the amount of mercury in the urine shows marked variations from day to day, due apparently to varying conditions affecting absorption from the intestine. With suddenly increased absorption there is danger of mercurialism.[9]

The results of the treatment of syphilis by intramuscular injections of mercurial salts are more rapid after the use of a soluble than an insoluble preparation. The soluble salt is more rapidly efficacious because it is possible to more quickly mercurialize the patient owing to the more rapid absorption and less local reaction. Excretion begins at once, and if given each day elimination rises gradually and regularly, the amount gradually decreasing when

[6] Jour. Cutan. Dis., xxxiii, 1915, p. 819.
[7] Meyer and Gottlieb, Pharmacology; Clinical and Experimental.
[8] Ibid.
[9] Ibid.

stopped. Unfortunately, to be efficient, the injections should be given daily in doses of $\frac{1}{10}$ to $\frac{1}{5}$ grain. This, of course, can be done in hospital wards where patients are under continuous observation, but in dispensary practice and private work it is found to be impracticable because of the frequent visits necessitated. For this reason the insoluble salts have come into use. They form a depot of absorption and require to be administered only at weekly intervals. The rate of absorption is of course much slower, the local reaction more intense and the therapeutic effect slower and less reliable. From animal experiments Schamberg, Kolmer, and Raiziss found that at the end of six or seven weeks almost 50 per cent. of the mercury of insoluble preparations may be unabsorbed at the site of injection. Cases have been reported in which patients weeks or months after treatment suffered from mercurial poisoning when sudden absorption from several foci took place. The elimination curve does not indicate a gradual regular saturation, but maximal elimination occurs on the day of injection and sinks immediately, rising with each new injection. We are now treating all of our cases at the City Hospital with soluble preparations, and we find that some of the most refractory rashes, like the early follicular syphilide, disappear in from two to three weeks even when salvarsan is not given. They are also especially valuable in cerebrospinal syphilis when a rapid effect is desired.

Conclusions. The fate of the syphilitic individual depends upon the early diagnosis of his infection and the intensity with which treatment is carried out in the first six months. In the accomplishment of this purpose the modern aids to diagnosis have rendered great service. The dark-field illumination furnishes a valuable means of corroboration in all suspicious genital sores and assists in determining the nature of extragenital lesions which may simulate chancre. It should be employed in every case of chancroid to confirm or rule out the possible coincident infection with the Treponema pallidum.

The Wassermann test fills a large field of usefulness not only as a diagnostic medium but as a guide to the effect of treatment and criterion of cure. It is of special value in all conditions of obscure etiology referable to the cardiovascular system, cerebrospinal system, or viscera in which syphilis might be a factor, and in cases with an indefinite clinical picture, such as neurasthenia, febrile attacks, rheumatic pains, etc. Its interpretation is of great importance and requires as much training and experience on the part of the practitioner as does the interpretation of the physical signs.

The examination of the spinal fluid enables us to determine the activity of the luetic process in the brain or cord, to distinguish the various pathological types affecting the central nervous system, and in many cases to differentiate between these and non-syphilitic affections. Recent investigations have shown that an analysis of the spinal fluid is not complete unless the Lange or colloidal gold

test is performed in addition to the Wassermann reaction and a cytological and chemical examination. Its chief usefulness lies in distinguishing true paresis from types of cerebrospinal syphilis which simulate it and in diagnosing incipient cases before the clinical syndrome is established. This affects chiefly the prognosis, as our main hope lies in the early diagnosis and treatment of these cases, for when degenerative stigmata are already present the outlook is not so encouraging, for sooner or later relapses occur.

In primary syphilis where the spirochetes are demonstrated and the Wassermann reaction is negative it is possible to cure syphilis with salvarsan alone. It cannot be determined how many doses are required, and as there may be a dissemination of spirochetes even in the presence of a negative Wassermann reaction it is better, therefore, to err on the side of safety and to give at least eight to ten doses and follow this with mercury for perhaps six months.

In secondary syphilis when the early rash is present and the Wassermann positive it is better to precede the salvarsan with several injections of a mercurial salt, preferably a soluble one, on account of the economy of time. In this way an effect is produced on the spirochetes, and when salvarsan is given the temperature reaction and an intensification of the rash—that is, a Herxheimer reaction—can be avoided. After the salvarsan is begun the treatment is to be continued in the manner outlined in the body of the article. The dermatologist and syphilologist should keep in mind the possibility of the involvement of the nervous system in secondary syphilis, and a complete status should be made when the patient comes under observation so that this record can be compared with any subsequent developments. In this way we are often enabled to detect the very earliest changes which manifest themselves objectively in the nervous system. The most frequent are irregularity of the pupils, persistent headache, and optic neuritis, or auditory disturbance.

In latent syphilis with a positive Wassermann reaction an investigation should be made of the cardiovascular and of the nervous systems or of previous involvement of any of the viscera, as, for instance, syphilitic hepatitis. In cardiovascular syphilis the prolonged use of mercury in connection with potassium iodide is probably of more value than the haphazard use of occasional doses of salvarsan. In other words, in tertiary syphilis with a persistent positive Wassermann reaction without involvement of the central nervous system the beneficial effects of potassium iodide cannot be too strongly insisted upon. In bone and periosteal lesions attended by severe pain there is no drug in the Pharmacopœia that produces so rapid an effect in relieving the pain and reducing the neoplasm.

The criteria of cure are a negative Wassermann reaction for at least a year continuing so after a provocative injection of salvarsan and a normal spinal fluid, with the exceptions which have been noted.

TABLE I.—RESULTS OF TREATMENT IN CASES OF EARLY INFECTION.

Case.	Duration of infection.	Treatment.						Serological result.	Clinical or serological relapse.	Provocative salvarsan.
		Begun.	Ended.	Amount and kind.						
				Salvarsan injections.	Mercury.		Mixed.			
					Injections.	Rubs.	Oral.			
J. M.	2 months	July 15, 1910	July 25, 1911	1	19	35	3 months	...	June 9, 1911 –	None	June 24, 1914 –
G. S.	9 weeks	Feb. 2, 1911	Oct. 1, 1913	2	..	60	3½ months	...	Dec. 6, 1911 –	"	Dec. 17, 1913 –
C. E.	2 months	Feb. 11, 1916	Sept. 15, 1912	2	One and a half years			...	April 26, 1911 –	"	June 17, 1914 –
W. C.	2 months	Nov. 17, 1910	Dec. 22, 1910	3	..	..	..	...	Feb 4, 1911 –	"	Dec. 23, 1914 –
H. N.	2 weeks	Nov. 20, 1911	July 9, 1912	4	17	..	..	...	Oct. 6, 1912 –	"	Mar. 28, 1914 –
B. S.	10 weeks	Nov. 24, 1913	Dec. 19, 1914	17	47	..	..	...	Sept. 14, 1914 –	"	Dec. 6, 1915 –
A. N.	7 months	Sept. 27, 1913	Sept. 9, 1914	17	41	..	..	...	Oct. 9, 1914 –	"	Dec. 28, 1915 –
J. G.	6 weeks	Feb. 19, 1908	Oct. 21, 1910	..	31	..	1 year	1 month	Jan. 25, 1911 –	"	Feb. 26, 1915 –
S. W.	6 weeks	Dec. 30, 1910	July 27, 1911	2	13	10	..	...	June 11, 1913 –	"	
R. Y.	3½ months	Jan. 14, 1911	July 9, 1912	7	..	..	..	...	Mar. 11, 1911 –	"	
G. B.	5 weeks	April 10, 1911	Jan. 15, 1912	3	..	9 weeks	2 months	...	May 4, 1912 –	"	
T. C.	1 month	Oct. 21, 1912	Nov. 9, 1912	4	..	..	..	...	Always –	"	
H. C.	4 weeks	Jan. 23, 1914	Oct. 30, 1914	10	21	..	..	...	April 18, 1914 –	"	
G. C.	5 weeks	July 31, 1914	April 14, 1915	10	24	..	..	...	Nov. 18, 1914 –	"	
C. A.	6 weeks	Dec. 15, 1913	Oct. 17, 1914	6	25	..	..	...	Always –	"	
J. C.	2 months	June 13, 1914	Mar. 2, 1915	9	25	..	..	...	Sept. 17, 1914 –	"	
H. N.	4 months	Nov. 16, 1913	May 29, 1914	13	13	..	..	...	May 27, 1914 –	"	
R. G.	8 weeks	Aug. 16, 1913	June 2, 1914	12	19	..	..	...	June 13, 1914 –	"	
W. C.	6 weeks	Aug. 15, 1905	Oct. 6, 1909	..	50	..	7 months	6 months	Oct. 24, 1913 –	"	

TABLE II.—RESULTS FOLLOWING PROVOCATIVE INJECTION.

Case.	Date of infection.	Wassermann before treatment.	Treatment.						Wassermann.	Clinical or serological relapse.	Provocative salvarsan.
			Begun.	Ended.	Amount and kind.						
					Salvarsan injection.	Mercury.					
						Injection.	Rubs.	Oral.			
P. A.	1886	4+	Dec. 2, 1909	June 18, 1912	1	61	...	...	Dec. 6, 1913 −	None	Jan. 14, 1914 ++++
J. B.	1897	(?)	1897	1900	..	...	...	2½ years	Oct. 30, 1912 −	"	Nov. 12, 1912 ++++
C. M.	1910	(?)	Oct. 19, 1914	Feb. 1, 1915	..	50	...	...	April 3, 1915 −	Has tabes	April 14, 1915 ++++
J. A.	1901	(?)	1901	1905	..	1½ years	3 years	...	Mar. 15, 1916 +	Gummata	Mar. 23, 1916 ++++
E. K.	Hereditary, 7 years old	+	No treatment Parents syphilitic	No symptoms	..	..	...	...	.....	....	Provoc. KI Oct. 7, 1915 Wassermann Mar. 1, 1916 ++++
J. C.	1890	(?)	1890	1899	..	..	8 years	6 months	1909 −	None	Jan. 23, 1912 −
W. H. S.	June, 1913	4+	Dec. 2, 1913	Oct. 1, 1914	16	44	...	...	Nov. 24, 1914 −	"	Sept. 12, 1915 −
T. P.	(?) third stage	4+	Sept. 29, 1913	April 11, 1914	16	42	...	...	May 11, 1914 −	"	Oct. 20, 1915 −
J. E. H.	Feb. 2, 1914	4+	April 14, 1914	Dec. 1, 1914	16	38	...	...	Jan. 25, 1915 −	"	Nov. 27, 1915 −
S. D.	(?) third stage	4+	Sept. 24, 1913	Sept. 15, 1914	17	49	...	...	Oct. 16, 1914 −	"	Feb. 9, 1916 −
G. E. G.	(?) third stage	4+	May 19, 1914	July 9, 1915	13	56	...	...	July 9, 1915 −	"	Dec. 20, 1915 −
M. R.	May, 1914	4+	July 8, 1914	June 15, 1915	15	46	...	...	Feb. 3, 1915 −	"	Dec. 19, 1915 −
B. S.	Miscarriages	4+	Dec. 26, 1913	Feb. 30, 1915	19	47	...	...	Mar. 2, 1915 −	"	Feb. 7, 1916 −
B. S.	Sept., 1913	4+	Nov. 24, 1913	Dec. 1, 1914	17	47	...	...	Sept. 14, 1914 −	"	Dec. 6, 1915 −
C. B.	April, 1914	4+	Dec. 29, 1914	Dec. 15, 1915	15	45	...	...	July 22, 1915 −	"	Feb. 8, 1916 −
A. N.	Jan., 1913	4+	Sept. 27, 1913	Sept. 9, 1914	17	51	...	...	Oct. 9, 1914 −	"	Jan. 24, 1916 −
A. Mc.	May, 1914	4+	July 12, 1914	July 15, 1915	17	42	...	...	Feb. 15, 1915 −	"	Jan. 3, 1916 −
T. M.	1908	4+	Oct. 21, 1912	July 7, 1913	9	22	...	...	Sept. 11, 1913 −	"	Dec. 27, 1915 −

TABLE III.—INTRACTABLE REACTIONS AFTER PERSISTENT TREATMENT.

Case.	Date of infection.	Wassermann before treatment.	Treatment.					Wassermann after treatment.	Clinical relapses during treatment.	Remarks.
			Amount and kind.				Duration.			
			Salvarsan injections.	Mercury.		Mixed.				
				Injections.	Rubs.					
W. Z.	Nov., 1911	++++	14	45	...	....	1½ years	++	None	Clinically negative.
B. H.	April 26, 1913	++++	16	36	...	....	1 year	+	"	Clinically negative.
F. G.	April, 1912	++++	20	26	...	....	1½ years	+	"	Clinically negative.
A. R.	1909	++++	22	36	4 months	4 months	2 years	++++	"	Clinically negative; spinal fluid negative.
W. W.	1899	++++	16	31	...	8 months	2½ years	++++	"	Has remains of hepatitis.
L. H.	Dec., 1912	++++	15	101	4 months	18 weeks	2¼ years	++	"	Has aortitis.
I. D.	Mar., 1913	++++	12	72	...	6 months	2½ years	+	"	Has aortitis.
J. B.	Denied	++++	17	10	...	6 months	1½ years	++++	"	Large aneurysm present.
R. H.	1907	++++	23	30	88	16 weeks	2 years	++++	"	Optic atrophy; spinal fluid positive.
F. M.	1903	++++	9	32	...	....	7 months	++++	"	Tabes; spinal fluid positive.
G. M.	1902	++++	20	60	6 months	1 year	2½ years	++++ ++++	"	Spinal fluid positive; cerebrospinal syphilis.
E. R.	1904	++++	31	40	...	....	1½ years	++++	"	Has paresis; spinal fluid positive.
M. D.	Congenital 29 years ago	++++	18	36	...	2 years	3 years	++++ ++++	"	Remains of keratitis; deafness; spinal fluid negative.

THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.[1]

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In order to discuss treatment of syphilis of the central nervous system it is essential to orient ourselves in the various problems which this disease presents.

It is now well established that spirochetes circulate in the blood of practically all patients in the late primary and early secondary stages, and during this period the central nervous system is frequently involved. In fact, with the early and almost universal dissemination of the infectious agent it is difficult to conceive how any organ escapes infection. It is not alone the presence of the spirochetes, but the reaction of the tissues toward them which determines the type of infection. It is recognized that spirochetes can lie dormant in the tissues, in latent cases, with practically no cellular reaction about them. Different observers report wide variation in the relative frequency with which the cerebrospinal fluid shows evidence of alteration in the secondary period. Ravaut[2] found abnormalities, with pleocytosis or globulin excess, or both, in 67 per cent. of cases, Altmann and Dreyfus[3] in 66 per cent. Gennerich[4] states that at some time, either before or during intensive salvarsan treatment, 90 per cent. of his cases in the secondary period showed some abnormality of the cerebrospinal fluid. Ellis and I[5] found only 33 per cent. of abnormal fluids in untreated patients in the secondary period, but had the fluids in all patients in the secondary period been included in our statistics the percentage would be somewhat higher.

From the above observations it is evident that infection of the central nervous system occurs in a large proportion of cases of secondary syphilis. Since we know that only a small proportion of syphilitic patients show nervous involvement in later years it is evident that in many cases this infection must undergo spontaneous resolution. This phenomenon corresponds with the course of syphilis elsewhere in the body, and is probably due, in part, to a tissue immunity which develops as a result of prolonged contact between parasite and host. As a result of this tissue immunity the secondary eruption disappears, and cutaneous relapses may never recur even in untreated patients. If, however, cutaneous manifes-

[1] Read at the Tenth Triennial Session of the Congress of American Physicians and Surgeons, Washington, May 9, 1916.
[2] Ann. de dermat. et de Syph., 1903, S. 4, iv, 1.
[3] München. med. Wchnschr., 1913, lx, 464.
[4] Die Liquorveränderungen in dem einzelnen Studien der Syphilis, Berlin, 1913.
[5] Jour. Exp. Med., 1913, xviii, 162.

tations do recur they become more and more localized, tend to group, and to involve deeper structures, with finally gummatous changes.

A similar process appears to occur in the central nervous system. Following the initial inflammation the organisms deposited in the meninges during the period of spirochetemia are usually destroyed; but in some cases they remain latent only to become active after a period of months or years. This is the usual course of syphilitic infection in untreated or poorly treated cases. The character of the picture may, however, be altered by the institution of intensive treatment. It has long been observed that cases of primary syphilis, relapsing after unsuccessful attempts at abortive treatment with mercury, are liable to show severe skin lesions. Similar deep nodular or ulcerative lesions are frequently seen in the relapses following inadequate salvarsan treatment. This phenomenon of increased severity noted in relapsing lesions of the skin occurs also in the central nervous system, and explains the occurrence of meningitis with cranial nerve paralysis in many of the inadequately treated cases of secondary syphilis. In these patients the greater part of the infecting organisms have been destroyed by the remarkable spirocheticidal action of salvarsan. This has, moreover, been accomplished so rapidly that the usual tissue immunity which develops as a result of prolonged contact between parasite and host is lacking. As a result a small focus of spirochetes, tucked away safely in the tissues of the central nervous system, and thus escaping the spirocheticidal action of the salvarsan can develop in the susceptible host with great rapidity and severity. The severity of the meningitis is evidenced by the cerebrospinal fluid, which shows a marked pleocytosis, considerable globulin excess, and usually a strongly positive Wassermann reaction. The Wassermann reaction in the blood is frequently negative, showing how well the active syphilis is limited to the central nervous system. The failure to recognize this possibility of active meningitis in the early stages of syphilis, with a negative Wassermann reaction in the blood, may result in the failure to resume treatment at a most critical period. It should be emphasized that the development of this condition is due to inadequate intensive treatment, and that a few doses of salvarsan, without continued treatment, may result in more severe nervous manifestations than if milder therapy had been applied.

The recognition of the early involvement of the central nervous system is important not only because of the possibility of the development of an early meningitis but also from the stand-point of prophylaxis of the later and more destructive conditions. The best treatment of brain gummata, tabes, and paresis will always be their prevention.

Before starting treatment in any case it is well to try to recognize the character of the involvement, for the subsequent therapy is, to a certain extent, determined by the type of manifestation. These

manifestations depend upon the tissues involved, and upon the reaction of those tissues to the irritative effect of the spirochetes. The disease may implicate the meninges, bloodvessels, or parenchyma. While it is conceivable that any one of these structures may be affected alone, still the intimate relation of one structure to the other makes it almost impossible for one to be diseased without the others sharing to a certain extent in the pathological process. There is, however, a type of nervous disease due to syphilis in which the infection seems to involve the vessels in the form of an endarteritis. In this instance the cerebrospinal fluid shows little if any abnormality, and the symptoms are referable to the arterial sclerosis of the cerebral vessels rather than to actual interstitial or parenchymatous disease. The response of this type of case to treatment depends upon the extent to which the endarteritis can be favorably affected and not upon the resolution of a syphilitic exudate in the meninges.

Following the demonstration of the Treponema pallidum in paretic brains a new classification of lues of the brain and cord has arisen. This comprises (1) interstitial types, which include the lesions previously classified under cerebrospinal syphilis, and (2) parenchymatous types, which include paresis and tabes dorsalis.

In both the interstitial and parenchymatous forms the one common lesion is the perivascularitis which may vary, to a wide degree, from a simple mantling of the vessel to a collection of cells in the form of miliary gumma, and when combined with a similar process in the meninges may result in large gumma formation. In the interstitial forms, which include meningitis, menigo-arteritis, and gumma, the disturbance in function is due either to an actual destruction of the nervous elements or to a cutting off of nutrition to the nerve tracts and centers. This latter condition may be brought about by the narrowing of vessels and compromising of the lymphatic spaces to the edema surrounding active inflammation and to pressure from the tumors. In fact, the remarkable improvement of many of these cases under treatment can be explained only on the basis that the pathological process has been largely limited to the vessels and meninges. In the parenchymatous forms the outstanding picture is degeneration of nervous elements combined with symptoms of irritation of these structures. Unfortunately it is impossible to examine microscopically the tissues in these parenchymatous forms until late in the disease, when the degeneration is far advanced. But even at this time perivascularitis and focal meningitis are usually seen, and it does not seem unreasonable to consider that much of the degeneration is secondary to a disturbance of the nutrition of the cell or axis-cylinder, which has resulted from a blocking of the perivascular, perineural, or perineuronal lymph spaces by the cellular exudate.

In paresis the presence of the spirochete in the brain substance

may by the liberation of toxins result directly in the death of the cell. In tabes dorsalis, however, the active inflammatory process is not usually found in the most obviously degenerated areas, namely, the columns of Goll and Burdach, but rather in the dorsal roots and in the meninges surrounding them. An example of the earliest stages of tabes is the interesting case of Larkin[6] in a patient with "sciatica," girdle pains, pleocytosis, and positive Wassermann reaction in the cerebrospinal fluid, who died from a ruptured aortic aneurysm and whose postmortem showed insular sclerosis of the posterior nerve root, with accompanying syphilitic meningitis but no column degeneration.

From the examination of the retina and optic nerves of many cases of optic atrophy in tabetics and paretics, Stargardt[7] concluded that the atrophy is secondary to a round-cell infiltration of the intracranial portion of the optic nerve and the chiasm. In those cases with a segmental optic atrophy there was only a partial infiltration of the optic nerve. He argues against the view that tabetic optic atrophy is a system disease due to a toxin, but believes rather that it is an example of the reaction of the nervous tissue to the spirochete, for in several of his cases the auditory and olfactory nerves were similarly infiltrated. Spiller[8] showed that the essential lesion in tabetic oculomotor paralysis is due to a round-cell infiltration in the oculomotor nerves at their point of emergence from the medulla, which he thinks is probably secondary to the pial infiltration in this region. He considers that the nuclear degeneration is usually secondary to the inflammation of the nerve stem. Thus it appears that the classification of the various tabetic atrophies as primary is only an attempt to explain them in terms of the older opinion that these diseases were parasyphilitic in nature. As a matter of fact, they all appear to be secondary to a chronic syphilitic meningitis.

Chronicity is probably an important element in the development of parenchymatous syphilis. The outstanding symptoms of most cases of tabes or paresis develop from the tenth or twelfth year, after the primary infection. Upon careful questioning of many of these patients it will be found that some single symptom, such as pain or isolated nerve paralysis, often transitory in character, has occurred years previously, and their nature is often recognized only after the disease is well developed. These facts point to the probability that a low-grade inflammation with subsequent atrophy has been going on for years, and only after a sufficient number of tracts or centers are involved to interfere with the patient's usual activities does he seek the aid of the physician. On the other hand,

[6] Cited by J. A. Fordyce, Harvey Lectures, 1914–15, Series X.
[7] Allg. Ztschr. f. Psych., 1912, lxix, 735.
[8] Jour. Nerv. and Ment. Dis., 1915, xlii, 15.

the majority of cases of the interstitial type develop in the first three years after infection. The course is more rapid and the symptoms appear with greater violence, no doubt due to the fact that there is a more extensive and rapid development of the meningeal and perivascular exudate.

In both tabes and cerebrospinal syphilis, then, we are dealing with diseases of a similar nature. The variation in the manifestations seems to depend upon the difference in the rapidity and degree of development as well as upon the localization of the inflammatory process. In tabes the infiltration being less intensive and slower, the picture of degeneration is brought more vividly into the foreground. The spinal fluid in the two diseases is practically the same, even to the type of curve in the gold reaction. Both also respond to specific treatment in much the same manner, although at a different rate, and while the symptoms due to irritation are improved, those due to degeneration are little if any affected.

In paresis, on the other hand, we appear to be dealing with a disease which is not strictly comparable with the two just discussed. There are certain points of similarity, namely, in the meningitis and perivascularitis. The direct action of large masses of spirochetes in the substance of the cerebral cortex may possibly result directly in the destruction of cortical cells and fibers. The peculiar type of curve in the gold reaction, moreover, points to some essential difference between this disease and tabes. The difference in response to treatment is also most striking. While most cases of tabes will show the favorable influence of treatment both in the spinal fluid and in marked and persistent clinical improvement, the response of most paretics to a similar or more intensive treatment is much less noticable, and the ultimate results are usually discouraging. Whether this difference in response is due to difference in accessibility of the active lesion or to the fact that in paresis the disease attacks portions of the central nervous system, which are more essential to the orderly carrying on of vital functions, are questions which are as yet unanswered.

It goes without saying that the best preventive of syphilis of the central nervous system is the prophylaxis of syphilis; but this problem is far from solved. Next in importance is the proper treatment of syphilis in the early stages. It should be emphasized at this point that no case should be released from treatment until the cerebrospinal fluid has been shown to be normal, insofar as pleocytosis and Wassermann reaction are concerned. Whether a slight excess of globulin is an indication for continuation of treatment, if all other abnormal elements are absent, is still an open question. In a number of patients with meningitis in the secondary period, whom we have followed for several years, the globulin is still in excess, although all other evidence of the disease had been absent for three or more years.

Even with the present diagnostic methods and several effective therapeutic agents it is safe to say that a fair proportion of patients with syphilis are poorly treated, and probably a majority of them are released without lumbar punctures. The failure of many patients to be followed until cured is due to several causes: (1) the patients fail to realize the importance of proper treatment in the prophylaxis of later disease and discontinue their treatment of themselves; (2) there is still a surprising lack of facilities in dispensaries for the proper treatment of syphilis; (3) many physicians fail to realize the long systematic course that is required to eradicate the disease completely; (4) there are many cases of innocent syphilis and syphilis with slight, if any, early manifestations which go untreated and later develop serious nervous lesions. (Table I.)

TABLE I.

Mattauschek and Pilcz	Total cases 4134
Developed paralytica dementia	198 = 4.8 per cent.
" tabes dorsalis	113 = 2.7 "
" cerebrospinal lues	132 = 3.2 "
Total	443 = 10.5 "

EFFECT OF TREATMENT.

	None.	1 course.	Repeated energetic
Number of cases	100	134	924
Developed G. P.	25 = 25 per cent.	31 = 23.1 per cent.	30 = 3.2 per cent.
" tabes	11 = 11 "	16 = 11.9 "	25 = 2.7 "
" cerebrospinal lues	3 = 3 "	21 = 15.6 "	71 = 7.6 "

	Poorly treated 1880–84.	Better treated 1895–99.
Number of cases	617	1139
Developed G. P.	60 = 9.7 per cent.	37 = 3.2 per cent.
" tabes	22 = 3.5 "	16 = 1.4 "
" cerebrospinal lues	15 = 2.4 "	28 = 2.4 "

While the incidence of cerebrospinal involvement in syphilis varies in different races and in the different sexes the experiences of Mattauschek and Pilcz[9] is representative. These authors followed 4134 cases of syphilis in officers in the Austro-Hungarian army who were infected between 1880 and 1900. These cases were followed until 1912. The results of these investigations are shown in Table I. A striking feature of the table is the difference in the percentage of cases that developed tabes and paresis who were untreated or poorly treated compared with those who had been energetically treated. Practically a quarter of the poorly treated cases developed paresis contrasted with a little over 3 per cent. of those who were well treated. Similarly from 11 to 12 per cent. of the poorly treated ones developed tabes, while only a fifth of this proportion of well-treated patients developed this disease. A single course of treatment seemed to increase the liability to the cerebrospinal form of

[9] Ztschr. f. ges. Neur. and Psych., 1910–11, iv, orig., 697; 1913, xv, 608.

lues. This observation is of added interest in view of our present knowledge of the results of insufficient salvarsan treatment on the development of cerebrospinal syphilis already discussed in an early part of this paper. A similar parallelism between early efficient treatment and diminished incidence of tabes and paresis is seen in the last part of the table. In the period between 1880 and 1884 the treatment was relatively insufficient, while in the period between 1895 and 1899 there was an improvement in the general treatment of the disease with a corresponding decrease in the incidence of parasyphilis. It is striking that the incidence of cerebrospinal syphilis in the two groups is the same.

If the difference between poor application of mercury and fairly efficient application is so marked it is reasonable to expect that under the modern intensive treatment with both mercury and salvarsan the incidence of parasyphilis should be even more markedly reduced. From a simple, economic point of view the State should provide for the proper treatment of early syphilis, for upon the State eventually falls the cost of caring for the paretic and, to a less extent, for the tabetic.

From the standpoint of prophylaxis of tabes or paresis it is also important to realize that they frequently develop slowly, and that signs or symptoms are often present for years before the disease is fully manifest. Lately more attention has been directed to the monosymptomatic forms of syphilis of the central nervous system. Some authors claim that these forms are more frequent today than formerly, and that tabes is assuming a milder character; but it is more probable that their detection is due to refinement in diagnosis. While fairly numerous cases are reported in which the monosymptomatic forms remained free from further symptoms for many years in spite of lack of treatment it is wiser to regard all such cases as being early forms of late serious disease. Years ago Erb called attention to the importance of ophthalmoplegia interna as a forerunner of tabes or paresis and he has followed several cases from the appearance of a simple eye lesion to the fatal ending in paresis. Many patients with tabes give a history of a transitory squint which was present years before any other symptom. Often the condition has improved after the administration of a small amount of iodides or mercury and the patient has been allowed to escape from further observation. Auditory nerve lesions are also described early in tabes as well as in cerebrospinal syphilis. These patients usually consult the otologist. It is important for the specialist to realize that these isolated nerve lesions are a part of the general disease, syphilis of the central nervous system, and that they are usually manifestations of a basilar meningitis. Surgeons also see early manifestations in abdominal disturbances. Nuzum[10]

[10] Jour. Am. Med. Assn., 1916, lxvi, 482.

recently reported that among a thousand cases of tabes admitted to Cook County Hospital, 87 had previously undergone laparotomy because of the mistaken diagnosis of their abdominal pain. It is important to remember that gastric crises, either mild or severe, may be present as the first manifestation of tabes for years before full development of the disease. Other single symptoms which are often present for a longer or shorter period are bladder disturbances, lightning pains in the leg, and "rheumatism." The general practitioner or the specialist should recognize the nature of these symptoms and place the patient under proper treatment, for it cannot be emphasized too strongly that prevention of degeneration is worth vastly more than the treatment of symptoms once they have fully developed.

The examination of the blood and cerebrospinal fluid is of the greatest help in clearing up the diagnosis in doubtful cases, and to a certain extent in determining the type of syphilitic involvement of the central nervous system. While these examinations are of great value, they do not replace but only complement a careful clinical examination. I cannot do better than quote Miller:[11] "The value and interpretation of any laboratory method should always be based upon the most careful clinical study of the cases in which it is applied;" and also, "Any normal reaction in the cerebrospinal fluid may be present or absent in any luetic involvement of the brain or spinal cord." There are certain combinations of reactions which occur with sufficient frequency in certain conditions to render such findings highly significant. An increase in globulin is found in most cases of any type; it is most marked in paresis, but may be equally intense in secondary meningitis. Pleocytosis is usually the most intense in meningitis in the secondary stage, but counts above 100 are not infrequent in later cerebrospinal syphilis, tabes, and paresis. The type of curve given by the Lange gold reaction in cerebrospinal lues and tabes is of confirmatory value, but its great field of usefulness seems to be in differentiating paralytica dementia from these two conditions. The fact that the fluid from a patient with a clinical diagnosis of tabes, or cerebrospinal syphilis, gives a paretic curve does not militate against the reaction, for it is well known that between 10 and 15 per cent. of tabetics develop paresis, and at time it is impossible to differentiate between cerebral syphilis and paresis. If future observations confirm what now seems probable, namely, that a paretic curve obtained with the spinal fluid of patients clinically not paretic points to a possible development of this disease, it will be of importance in prognosis and of value in determining why symptoms of mental disorder appear in spite of vigorous and prolonged treatment.

At this point it is well to emphasize the value of constant methods

[11] New York State Jour. Med., 1915, xv, 376.

in making the various tests on the cerebrospinal fluids. Dilutions for cell counts should be made immediately. The necessity of proper solutions for the gold test have been pointed out by Miller[12] and his co-workers. Of no less importance is the titration of the strength of the Wassermann reaction in the spinal fluid. The designation of + + + + or negative Wassermann reaction in the fluid means but little unless we know the amount of fluid that was used in obtaining these readings. This is especially true when the effect of treatment is being estimated. For example, if 0.2 c.c. or 0.4 c.c. has been the only amount used to test the fluid a relatively mild treatment may change the reaction to negative. On the other hand, if only 1 c.c. has been used a more intensive treatment may not affect the reading, although, as a matter of fact, the reaction may be much weaker. The only way to judge accurately of the effect of treatment on the reaction is to test the fluid with diminishing amounts corresponding to values between 2 c.c. and 0.2 c.c. in the original Wassermann test (smaller amounts if necessary) and determine the point at which the reaction is completely positive. If, then, with a given amount of treatment the positive point has moved from 0.2 c.c. to 0.6 c.c. or higher, we know that the treatment is having some effect. This, of course, presupposes that constant methods are used at different times, for if a very sensitive method is used at one time and a comparatively unsensitive one at another the relative value of the two tests is lost.

The problem of treatment of syphilis of the central nervous system is complicated by the peculiarities of the subarachnoid space which, in addition to the larger spaces and cisterna, is directly continuous with the perivascular, perineural, and perineuronal lymph spaces. It does not seem unreasonable to suppose that the infection is carried by the cerebrospinal fluid along these channels, and the various meningeal and perivascular lesions can be most easily explained in this way. Frühwald and Zaloziecki,[13] in a review of their own cases and of the literature, have shown that the fluid is occasionally infectious in all stages from the secondary period to tabes and paresis.

The reaction to the spirochete is meningitis and perivascularitis. It is probable that the nerve cells and fibers obtain their nutrition to a considerable degree through these spaces, hence plugging of them with exudate not only compromises the nutrition of these structures but also probably increases the difficulties with which therapeutic agents are brought into contact with the exudate. At present it seems almost superfluous to recite the numerous experiments which prove the separateness of the subarachnoid space from the general lymphatic and blood-vascular systems. Antibacterial immune bodies, vital stains, and most drugs, when

[12] Johns Hopkins Hosp. Bull., 1915, xxv, 391.
[13] Berl. klin. Wchnschr., 1916, liii, 9.

administered by mouth or parenterally, do not reach the subarachnoid space in demonstrable quantities. It is true, however, that many drugs, given either by mouth or subcutaneously, do act on the central nervous system, but these drugs administered subdurally act in much smaller quantities. Many years ago Lewandowsky[14] showed that strychnin when injected intraspinally was ten times as effective as when injected intravenously. Similarly, sodium ferrocyanide subdurally was potent in one-hundredth the intravenous dose. The action of both drugs was at first local and then general, showing that they were rapidly diffused through the cerebrospinal fluid.

In many cases the general administration of mercury, iodides, and salvarsan affects favorably the course of syphilis of the cerebrospinal axis. This favorable influence is especially marked in the early forms of the disease. The tendency, however, of cerebrospinal syphilis to relapse in spite of energetic mercurial and iodide treatment has long been noted by syphilographers and neurologists, and the failure of most cases of tabes to respond to the antiluetic treatment of the presalvarsan era made therapeutic nihilists of most neurologists. Even the brilliant clinical improvement of most cases of cerebrospinal syphilis and tabes after salvarsan intravenously has not been followed by a parallel improvement in the cerebrospinal fluid. Dreyfus,[15] who gives courses of salvarsan of 4 to 6 gms. combined with ten to twelve injections of calomel or gray oil, notes that many such courses are necessary to eliminate all signs of the disease. In only 3 out of 125 cases of cerebrospinal syphilis did the fluid become normal after one or two courses. Gennerich,[16] who is famous for the intensity of his antisyphilitic treatment, says that he feels that all cases with meningeal involvement in any stage should have intraspinal treatment. Many observers report cases of cerebrospinal syphilis or tabes which, having come to a standstill, both clinically and pathologically, under general treatment, have shown renewed improvement under intraspinal therapy.

The desirability of subarachnoid therapy has been well established. The problem was to find some beneficial therapeutic substance which could be repeatedly introduced without injury to the delicate nervous tissue, for only by repeated and prolonged treatment can we hope to arrest any form of cerebrospinal lues permanently. Last year,[17] the writer reviewed the use of these various agents and the methods of their administration. Suffice it to say that the preparations which have stood the test of time are (1) the serum obtained from patients shortly after intravenous injections of

[14] Ztschr. f. klin. Med., 1900, xl, 480.
[15] München. med. Wchnschr., 1914, lxi, 525.
[16] Ibid., 1915, lxii, 1696.
[17] Swift, H. F., Jour. Am. Med. Assn., 1915, lxv, 209.

salvarsan; (2) serum to which small quantities of salvarsan have been added; (3) neosalvarsan in small quantities and weak concentration, and (4) mercurialized serum.

The direct application of mercury in the form of albuminate, as devised by Byrnes,[18] should theoretically be of value, and the reports seem to indicate that if the amount of mercury is kept under the irritating dose, beneficial results may be expected from its injection. It is well to call attention to the danger of repeated injections of mercurialized horse serum, which may lead not only to a general anaphylactic state to horse serum, but may cause the meninges to become hypersensitive to the foreign protein, and repeated injections over a number of months may lead to a chronic meningitis similar to the condition we are trying to combat.

The injection of neosalvarsan in concentrated solutions, as recommended by Ravaut,[19] or even in one pro mille solutions has been proved by numerous observers to be a dangerous procedure, since it is apt to be followed by various degrees of urinary retention and incontinence, rectal paralysis, paresthesia of the legs, ataxia and girdle sensations, and, in severe cases, by paralysis of the lower extremities and death. A given dose may be well tolerated several times, but later be followed by severe symptoms. Because of the uncertainty of unfavorable sequelæ, intraspinal injections of neosalvarsan should be given with extreme caution. Gennerich[20] lately reported that by using very dilute solutions he has been able to avoid these unpleasant symptoms. He, however, warns against the use of more than 0.5 mg. in spinal cord disease and not over 1 or 2 mg. in patients with paresis or syphilitic meningitis. Personally, I feel that repeated doses of this size are dangerous.

The addition of small quantities of salvarsan to serum as recommended by Ogilvie[21] was devised to give a known amount of salvarsan instead of the uncertain amounts in the serum salvarsanized *in vivo*. Marinesco and Minea[22] have noted that neosalvarsan is less irritating when diluted with serum than when dissolved in water or saline. Both Ogilvie and Fordyce,[23] however, have noted bladder disturbance and paresthesia in the legs when more than 1 mg. of salvarsan was added to the serum, and now I recommend that the dose should never be over 0.5 mg., usually less. With these quantities, intraspinal treatment has been followed by distinctly beneficial results.

The use of the serum of patients withdrawn after intravenous salvarsan injections has been criticized chiefly because of the small amounts of salvarsan it contained. We have found that the

[18] Swift, H. F., Jour. Am. Med. Assn., 1914, lxiii, 2182.
[19] Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, xxxvi, 752.
[20] Loc. cit.
[21] Jour. Am. Med. Assn., 1914, lxiii, 1936.
[22] Rev. neurol., 1914, xxii, 337.
[23] Jour. Am. Med. Assn., 1914, lxiii, 552.

majority of the sera one hour after an intravenous injection contained 0.01 mg. or more per cubic centimeter. When 12 to 20 c.c. of serum are used each treatment represents the injection of from 0.12 to 0.2 mg. of salvarsan. As above noted it is unsafe to inject intraspinally more than a fraction of 1 mg. of either salvarsan or neosalvarsan. The uncertainty of the dosage is an objection which cannot be overcome unless definite quantities of salvarsan are added.

The "autosalvarsanized serum" is, however, definitely spirocheticidal and the salvarsan is present in a colloidal combination with the serum which cannot be dialyzed through a celloidin membrane, as can salvarsan alone (Young,[24]). Salvarsan in this colloidal state is probably more slowly diffused out of the cerebrospinal fluid, hence is longer in contact with the syphilitic exudates. Moreover it seems to us that some of the beneficial effect from serum injection may be due to the introduction of the serum *per se*, for[25] we have obtained very interesting results from the intraspinal injection of non-salvarsanized both in diminishing pleocytosis and strength of the Wassermann reaction. The amount of the diminution in the Wassermann reaction is shown graphically in Table II. By reading from above downward the initial strength of the Wassermann reaction is indicated, while the reading from left to right gives the strength after treatment. The original strength of the reaction is also indicated by the heavy blocks. The number of treatments is indicated in parenthesis. It will be seen that 7 out of the 8 cases showed a diminution in the strength of the reaction, and in 3 of them it became negative with 1 c.c. fluid. During the period of observation none of the patients received any other treatment. If two of the cases, *A* and *B*, in which there was little or no effect, the treatment was continued with "autosalvarsanized serum," from other patients, with more marked diminution in the strength of the reaction, as is shown in part two of the chart. The severity of the infection in one of these cases is indicated by the fact that ten months' intravenous and intraspinal treatment was required before the reaction became completely negative. Four other patients were treated with intraspinal injections of salvarsanized serum, and in three of these the reaction became negative with 1 c.c. fluid. A résumé of the results in these 12 cases, treated only intraspinally with either normal or salvarsanized serum, shows that in half of them the reaction became negative with 1 c.c. of fluid, and in the others there was distinct diminution in the strength of the reaction. Two of these patients with gastric crises, Argyl-Robertson pupils, loss of tendon reflexes, bands of cutaneous anesthesia, and loss of deep pain sensation have been observed

[24] Biochem. Jour., 1915, ix, 479.

[25] The cases reported in this and subsequent tables were treated at the Rockefeller Hospital in collaboration with Drs. Ellis, Chesney and Stillman. A number of them were followed at the Presbyterian Hospital.

for over three years without any return of their trouble, and the fluids have remained normal. The results in these cases seem to prove that benefit is derived from intraspinal injections of serum. The explanation of these effects may be and probably is theoretical, but so are the objections to the treatment. The experimental facts stand and the injection of autosalvarsanized serum is followed by fewer permanent unpleasant effects than result from the intraspinal injection of any other antisyphilitic remedy.

TABLE II.—EFFECT OF INTRASPINAL INJECTIONS ON WASSERMANN REACTION IN CEREBROSPINAL FLUID.

Non-salvarsanized Serum.

W. R. before treatment.	W. R. after treatment.								No. of injections.
	++++					−−	++++	−−	
	0.2 c.c.	0.4	0.6	0.8	0.1	0.1	2.0	2.0	
0.2 c.c.		1 A	....	....	....	....	....	....	8
0.4 c.c.	....	1 B	....	....	....	....	....	....	7
0.4 c.c.	....	....	1	....	....	....	....	....	13
0.4 c.c.	....	....	....	....	1	....	....	....	12
0.6 c.c.	....	....		1	....	....	....	....	4
0.6 c.c.	....	....		....	....	1	1	....	17
0.6 c.c.	....	....		....	....	1	....	1	6
1.0 c.c.	....	....	....	....		1	....	....	6
Total 8	....	2	1	1	1	3			

Salvarsanized Serum.

W. R. before treatment.	W. R. after treatment.								No. of injections.
	++++					−−	++++	−−	
	0.2 c.c.	0.4	0.6	0.8	1.0	1.0	2.0	2.0	
0.2 c.c.		....	1	....	....	....	....	....	12
0.2 c.c.		....	....	....	....	1	....	....	11
0.2 c.c.		....	....	....	....	1	....	....	4
0.4 c.c.	....		1 A	....	....	....	....	....	4
0.4 c.c.	....		....	1 B	....	....	....	....	8
0.6 c.c.	....	....		....	....	1	....	....	8
Total 6	....	....	2	1	....	3			

In some patients the pain which follows the injection is so severe that the treatments must be discontinued, but such instances are the exception. The willingness of most patients to return for treatments over long periods is sufficient proof that the method is not too unpleasant for practical application.

A word as to technic: In most of our work at the Rockefeller Hospital the blood was withdrawn one hour after intravenous treatment and the serum diluted to 40 or 50 per cent. with normal saline and injected in quantities of 30 to 40 c.c. of this dilution. It was thought that the dilute serum was less irritating, but for the past two years at the Presbyterian Hospital we have bled the

patient one-half hour after intravenous treatment and injected 15 c.c. of whole heated serum without any more reaction than with the older method. Most of the patients now receive both the intravenous and intraspinal injections on the same day and return to their usual occupations the following day. In this way a minimum of time is required. It is necessary to keep some patients in bed for longer periods. In such instances we try to give the treatments on Saturdays so that the patients may be in condition to work by Monday morning.

It has seemed to us that the treatments are better borne if not repeated oftener than once in two weeks. This is especially true in tabetics or patients with spinal syphilis. In paretics or patients with cerebral syphilis the intervals may be shorter. At times it seems wiser to lengthen the intervals. It is well to bear in mind that a certain amount of irritation always follows the introduction of any foreign substance into the subarachnoid space, and the effect of this should be allowed to disappear before the treatment is repeated. A good rule to follow in any form of treatment of cerebrospinal syphilis is not to push the treatment so hard that the patient's general health is depressed. With each treatment there should be some improvement in the general condition; at least there should be no regression; for if a depressing treatment is repeatedly added to a more and more depressed condition the ultimate effect will be injurious rather than beneficial.

The treatment of the several forms of syphilis of the central nervous system presents different problems according to the stage of the disease and the individual patient. One general principle which should always be considered is that in any patient who shows evidence of involvement of the cerebral meninges or brain, salvarsan treatment should be preceded by a short course of mercury to prevent the possible occurrence of a Herxheimer reaction in the region of vital nervous centers. Fortunately such distressing reactions are rare, and can be obviated by proper preliminary treatment. If the presence of gummata is suspected a vigorous course of potassium iodide is often followed by marked improvement. It has seemed to us that the response of cases in the tertiary stage to salvarsan has been more marked and lasting if the courses of salvarsan have followed treatment with mercury and iodides. Gummatous exudates resolve under this preliminary treatment and the spirocheticidal effect of the salvarsan is more readily brought into play.

In the meningitis of the secondary period the response to alternate courses of salvarsan and mercury has been prompt and permanent in all of our cases. Gennerich[26] is of the opinion that all these cases respond more rapidly to combined intravenous and intraspinal

[26] Loc. cit.

therapy, and advises giving two intraspinal treatments after the cerebrospinal fluid has become normal. Following any form of treatment in this condition the cerebrospinal fluid should be examined in two or three months after treatment has been stopped, and every six months for two or more years thereafter to forestall relapses.

In the tertiary forms of the disease the so-called interstitial forms, alternate courses of mercury and iodides, and of salvarsan are usually followed by decided improvement, both clinical and in the condition of the cerebrospinal fluid. If possible the fluid should be examined after each course or each pair of courses. Not infrequently it will be found that the fluid has become normal after a few months' treatment. If so the prognosis is good and treatment should be conducted along general lines. On the other hand if the strength of the Wassermann reaction is the same or only slightly altered after four to six months of intensive general treatment it may be well to resort to intraspinal therapy.

In tabes dorsalis, because of the apparent sensitiveness of many cases to mercury, it is better to start the treatment with small intravenous doses of salvarsan, gradually increasing and giving a treatment every week for a course of six to eight injections. If at the end of this course the Wassermann reaction in the fluid is considerably weaker a course of mercury may be tried, followed by another course of salvarsan, alternate courses being given with periods of rest until the fluid is brought to normal. Many cases will be found, however, in which the strength of the reaction is only slightly altered by such a plan of treatment. The substitution of combined intraspinal and intravenous therapy in these patients will usually result in an improvement in the condition of the fluid. I am convinced that our aim should be to bring the fluids to normal and keep them there if we intend to speak of a cure of the syphilis. That this can be done in a majority of instances is shown in Table III, which gives the results in 37 cases followed for several years. All but 3 of these were tabetics, most of them well advanced. One was a case of diffuse myelitis, one of radiculitis, and one of opthalmoplegia interna. The cases are arranged in groups according to the original strength of the Wassermann reactions in the fluid, and the last finding is indicated in the vertical columns. In 30 of the cases (81 per cent.), the reaction became negative with 1 c.c. of fluid, but in 2 of these the reaction later increased in strength so that the final readings give 28 (75 per cent.) negative. Nineteen of these cases are also negative with 2 c.c., which is double the amount recommended by Hauptmann.[37] Of 18 cases which were negative with 1 c.c. or more, and have been followed from ten months to three and a half years without treatment, 14 remain

[37] München. med. Wchnschr., 1910, lvii, 1581.

negative with 2 c.c., 2 remain negative with 1 c.c., but positive with 2 c.c. One relapsed to positive with 1 c.c., and one with 0.6 c.c. In those cases in which the Wassermann reaction of the fluid increased in strength there was also a clinical relapse, while with a single exception in all the cases with persistent negative

TABLE III.—TABES DORSALIS. EFFECT OF TREATMENT ON WASSERMANN REACTION IN CEREBROSPINAL FLUID.

W. R. before treatment.	W. R. after treatment.									Amount of treatment.					
										Before W. R. neg. with 1 c.c., or until stopped.			Between neg. with 1 c.c.; neg. with 2 c.c. or until stopped.		
	++++						−−	++++	−−	Mos.	Int. ven.	Int. sp.	Mos.	Int. ven.	Int. sp.
	0.2 c.c.	0.4	0.6	0.8	1.0		1.0	2.0	2.0						
0.2 c.c.		1←	①	..	..		..	....	..	12	16	12			
0.2 c.c.		..	1	..	..		..	....	..	7	..	12 ns			
0.2 c.c.		..	..	..	1		..	....	..	24	32	15			
0.2 c.c.		..	..	..	..		1	....	..	1	..	4 ss			
0.2 c.c.		..	..	..	..		1	....	1	4	..	11 ns			
0.2 c.e.		..	..	..	..		1 →		1	8	12	10	8	10	3
0.2 c.c.		..	..	..	..		1 →		1	13	16	16	3	4	4
0.4 c.c.	....	1	..	..	..		..	....	..	6	..	13 ns			
0.4 c.c.	....	..	1	..	..		..	....	..	8	15	11			
0.4 c.c.	....	1	←	①	..		..	....	..	5	..	12 ns			
0.4 c.c.	....	..	..	..	..		1 →	1	..	11	21	7			
0.4 c.c.	....	..	..	..	..		1 →	1	..	15	24	18	4	6	5
0.4 c.c.	....	..	..	..	..		1 →		1	12	21	16	24	26	9
0.4 c.c.	....	..	..	..	..		1 →		1	29	35	18	8	8	
0.4 c.c.	....	..	..	..	..		1	....	1	1½	3	2	cont.		
0.4 c.c.	....	..	..	..	..		1	....	1	12	14	11	cont.		
0.4 c.c.	....	..	..	..	..		1	....	1	17	14	29	cont.		
					←										
0.6 c.c.	....	..	..	..	1		①	①	..	6	11	8	8	13	1
				←					←						
0.6 c.c.	....	..	..	1			①	→	①	..	..	..	8	17	17
0.6 c.c.	....	..	..	..	..		1	....	..	5	..	8 ss			
0.6 c.c.	....	..	..	..	..		1 →	1	..	8	18	7	14	26	19
0.6 c.c.	....	..	..	..	..		1 →	1	..	12	22	16	2	2	2
0.6 c.c.	....	..	..	..	..		1 →		1	8	..	17 ns	9	17	16
0.6 c.c.	....	..	..	..	..		1 →		1	4	6	5	6	9	9
0.6 c.c.	....	..	..	..	..		1	....	1	2	..	6 ns	4	8	
0.6 c.c.	....	..	..	..	..		1	....	1	5	8	6	11	21	
0.6 c.c.	....	..	..	..	..		1	....	1	4	7	..	11	20	10
0.8 c.c.	....	..	..	..	1		..	....	..	2	5	4			
0.8 c.c.	....	..	..	..	..		1	....	..	11	15	9			
0.8 c.c.	....	..	..	..	..		1	....	1	12(3)	20	5			
0.8 c.c.	....	..	..	..	..		1	....	1	3	6	6	cont.		
1.0 c.c.	....	..	..	..	..		1	....	..	1	2	2			
1.0 c.c.	....	..	..	..	..		1	....	..	1½	..	6 ss	cont.		
1.0 c.c.	....	..	..	..	..		1	....	1	1	2	2	cont.		
									→						
1.0 c.c.	....	..	..	..	..		1	①	1	1	3	2	cont.		
1.0 c.c.	....	..	..	..	..		1	....	1	1	2	1	cont.		
1.0 c.c.	....	..	..	..	..		1	....	1	1½	..	6 ns			
37	....	1	3	2	3		28	4	19						
....	....	2.7%	8%	5.4%	8%		75%	....	49%						

① = relapse.
ns = normal serum alone.
ss = salvarsanized serum alone.

fluids the disease has not progressed. In this one patient, who showed advanced tabes on admission, there has been an extension of the area of cutaneous anesthesia, and a neuropathic arthropathy of the shoulder joint has developed in spite of a normal fluid and negative blood Wassermann reaction. It will also be seen that there is a certain correlation between the initial strength of the

Wassermann reaction and the amount of treatment which was given before it became negative with 1 c.c. The number of cases in some of the groups is too small for averages to be of value, but in general the 1 c.c. or 0.8 c.c. group required from one to three months, the 0.6 c.c. groups about six months, and the 0.4 c.c. and 0.2 c.c. groups about twelve months. Not infrequently an equal or greater amount of treatment was required to change the reaction from negative with 1 c.c. to negative with 2 c.c.

In the presence of a rapidly advancing case of tabes or of optic atrophy, where it is desirable to arrest the progress of the disease, in an important organ, the institution of combined intravenous and intraspinal therapy at the beginning should be seriously considered, as rapidity of cure is the end to be accomplished.

Compared with the results in other forms of lues of the central nervous system the treatment of paralytica dementia has been disappointing. With the proof of the active syphilitic nature of this disease it was thought that a cure might be expected from intensive treatment; but there is something in the nature of the disease which apparently prevents the remedies from reaching the spirochete in sufficient quantities to eradicate them completely. It is true that most of the cases improve clinically, and in some of them there is a marked improvement in the condition of the spinal fluid. Still, with corresponding amounts of treatment this response is much less marked than in tabes. In addition there is a decided tendency for pleocytosis and Wassermann reaction to increase in intensity when treatment is discontinued. In two of our patients (see Table IV) there was at first almost as marked clinical improvement and diminution in abnormal elements in the cerebrospinal fluid as is seen in tabes. Both have had two relapses, and with each relapse the response to treatment has been less marked. This indicates that as the paretic process grows older it is less amenable to treatment, and probably explains the difference in results from State hospitals for the care of the insane and those from private physicians. In State institutions the cases are usually much more advanced than those which come under the observation of private institutions or practitioners. Thus Runge[28] reports 37.4 per cent. remissions, Raecke[29] 55.4 per cent. improved on salvarsan intravenously, Cotton[30] with combined intravenous and intraspinal therapy 58 per cent. arrested or much improved, and Ogilvie[31] 34 per cent. with complete remissions and 40 per cent. incomplete remissions, a total of 74 per cent. improved. In 4 of Ogilvie's cases both the blood and spinal fluids were brought to normal. When we compare these results with the number of remissions in the presalvarsan

[28] Deutsch. med. Wchnschr., 1914, xl, 998.
[29] Ibid., 1913, xxxix, 1348.
[30] Am. Jour. Insanity, 1915, lxxii, 125.
[31] Jour. Nerv. and Ment. Dis., 1916, xlviii, 263.

era 5.7 per cent.[32] or 7.4 per cent.[33] the treatment of paretics seems justified. The return of a paretic to his business, even though it be for only six months or a year, is often of vital importance to his associates and family. Compared with our therapeutic efforts in chronic cardiac or renal disease the results obtained thus far in paresis are decidedly encouraging, although in none of these diseases can we speak of a cure.

TABLE IV.—PARALYTICA DEMENTIA. EFFECT OF TREATMENT ON WASSERMANN REACTION IN CEREBROSPINAL FLUID.

W. R. before treatment.	W. R. after treatment.							Amount of treatment.		
	++++					−	++++	Moe.	Int. ven.	Int. sp.
	0.1	0.2	0.4	0.6	1.0	1.0	2.0			
0.1 c.c.	1	....	....	....	....	....	....	23(6)	11	8
....	1	....	....	....	....	....	....	18	31	18
....		....	1	....	....	....	....	20	38	26
0.2 c.c.	....		....	1	....	....	....	14	24	24
0.4 c.c.	....	....		1←	—①	....	....	36(11)	25	21
0.6 c.c.	....	....	....	1←	———	———	—①	30	50	32

In the treatment of syphilis of the central nervous system we should never forget the patient, and that he may be suffering from disease of other vital organs. If there is marked ataxia, Fraenkel's reëducation movements are useful; if he is emaciated, attention should be directed toward diet and general nutrition. Most patients with this form of disease show a certain amount of mental abnormality. Here psychotherapy is of value. In other words, treatment must be individualized, and while a general plan should be followed in the various forms of the disease, each case may demand a certain deviation to meet the peculiar conditions.

The objects of therapy are threefold: (1) the cure of disease; (2) the amelioration of symptoms; (3) the prolongation of life. With the possible exception of paresis all of these objects may be attained in most cases of syphilis of the central nervous system. To be satisfied with the attainment of the last two without attempting to attain the first is to fail to apply all the means at our disposal.

[32] Runge, loc. cit.
[33] H. L. Paine, Boston Med. and Surg. Jour., 1913, clxviii, 684.

THE PERSISTENCE OF ACTIVE LESIONS AND SPIROCHETES IN THE TISSUES OF CLINICALLY INACTIVE OR "CURED" SYPHILIS.

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Between the pathologist and the clinician there is always a certain antagonism of attitude with reference to the curability of any given disease. The clinician is, and naturally must be, more or less optimistic as to the results of therapy; and only with the greatest reluctance is he convinced of the weakness or total failure of his therapeutic means and methods. The pathologist, with the opportunities afforded him by tissue examination and autopsy, has the advantage of the very last word; and he becomes pessimistic as to ultimate cure because of his constantly recurring experience of finding evidences of active disease in cases clinically cured. This clash of opinion, clinical and pathological, is not shown elsewhere to such a degree as in the case of the veneral diseases, gonorrhea and syphilis. It took much work on the part of the pathologist to convince the practitioner that clinically cured cases of the so-called "lesser disease" were only apparent cures, and that the gonorrhea-infected individual remained for an indefinite period a germ-carrier, not only dangerous to himself but much more so to his future sex-partner. Likewise in the case of syphilis, therapeutic optimism has in recent years received severe blows at the hands of the pathologist. The frequency of latent syphilis of the heart, aorta, and central nervous system, the demonstration of spirochetes in conditions (paresis, tabes, etc.) until very recently regarded as parasyphilitic in nature and etiology, thus proving these conditions to be still active infections, have somewhat shaken clinical optimism. Cures once promised after a year of active treatment have passed through the two-, three-, and five-year limit, and now some clinicians are advising the syphilitic to take interval treatment over a period of many years or even throughout his lifetime if he will escape the uncertain chances facing everyone who acquires this disease. The wave of therapeutic optimism excited by salvarsan and the negative Wassermann reaction even now is subsiding.

It has been my experience as a pathologist to become very pessimistic as to the curative effects of any of the present-day methods of treating syphilis. Before the spirochete became an absolute pathognostic sign of the presence of this disease, certain myocardial, aortic, and testicular changes were regarded by the

pathologist as well-nigh positive proof of syphilis. The practically constant occurrence of these changes in the bodies of cases of clinically cured syphilis gave the pathologist good reason to believe that he was dealing with a still active process, although he had no means of proving this. The pathologist's judgment of these conditions is now confirmed by the demonstration of the spirochete of syphilis in such lesions. Localized tissue lesions of the smallest size and of the simplest nature (fatty degeneration, edema, etc.), that, a few years ago, would not, by any possibility, have been regarded as syphilitic, have been shown to be evidences of the local presence of spirochetes. I have elsewhere urged the fact that our conceptions of syphilis, both pathological and clinical, must be reshaped in the light of the spirochete; and that much work needs to be carried out along this line. The methods for the demonstration of this organism in the tissues should be made a part of the routine autopsy microscopic examination.

In my laboratory we have used Levaditi's original method with great success, and this is at the present time the only method of any value in demonstrating the presence of spirochetes in tissue. Its success will depend in the first place upon the freshness of the tissues. In my experience the spirochetes of syphilis quickly disappear from body tissues after the body becomes cold. Our necessity of having to make autopsies very soon after death has been a very great advantage in this respect. Tissues taken from a warm body within one to two hours after death and immediately fixed in 10 per cent. formol for at least twenty-four hours (better for three days), then put through the Levaditi method and blocked in paraffin give the best results. A formalin neutral in reaction and that has not been kept in wooden casks should be used. When properly prepared the number of spirochetes at times demonstrable in the tissues of congenital and active acquired syphilis is incredibly large. In the case of old latent syphilis the search for the organisms often becomes a prolonged hunt, and much time may be consumed in finding active lesions and demonstrating spirochetes within them. No one should think that this is wholly an easy matter. With an autopsy service of fifty to sixty cases a year the time of one assistant may easily be taken wholly for this work, should histological lesions of syphilis be found only in one-third of these. Such an arrangement I have had temporarily, but even with this advantage, the work has gone slowly enough. It may, however, be greatly expedited by confining the work to the organs, heart, aorta, testicles, and adrenals, most commonly the site of latent syphilis, and by making control blocks of all parts of the organ or tissue for quick survey in ordinary hematoxylin and eosin staining. Should such control blocks show lesions recognizable as those possibly due to the localization of spirochetes, the corresponding block in Levaditi preparation is then examined first before a gen-

eral examination of all the Levaditi blocks is made. If the blocks taken are small, as they should be, the neighboring Levaditi block is very likely to show some active process also. It may happen, however, that the hematoxylin and eosin sections alone show active lesions. The experiment of removing the paraffin and then putting the remaining portion of the block through Levaditi may be tried, but we have not found this procedure very satisfactory.

In the pathological service of the University of Michigan there were from 1912 to 1914, forty-one autopsy cases (one-third of the adult cases) that on microscopic examination showed active syphilis, determined either by the presence of the spirochetes or by characteristic tissue lesions. In the latter the spirochetes are being demonstrated as fast as the work can be carried out; and this has already been accomplished to such an extent in Class I, all cases in Class II, and in ten cases in Class III (one-half of the latent cases) as to leave no doubt of the correctness of the diagnosis in all of the cases. A preliminary report of this investigation was presented before the Association of American Physicians in 1914, and the publication of this paper has been delayed in the hope that we might be able to demonstrate the presence of spirochetes in all of the "cured" and unsuspected latent cases. This is only half completed. The labor has been much greater than at first anticipated. Six weeks were spent on the heart of one case before a small group of spirochetes was finally found. In eight cases in Class III, my assistant, Miss Wilson, demonstrated spirochetes in the heart muscle, but this work occupied a large part of a year.

The clinical history of a part of these cases gave no suspicion of the existence of a previous syphilitic infection; in others there was a doubtful or suspicious history of the disease; while in a smaller number the patient had been treated, or was at the time of death undergoing treatment, for syphilis. In the majority of cases, it will be seen, the clinical diagnosis, and consequently the treatment, entertained no suspicion of the existence of latent syphilis. In those cases in which syphilis was suspected or diagnosed the treatment in part had been regarded as adequate by the patient and previous physicians, but a new course of treatment had been instituted after coming to the hospital. In a small number of cases the treatment had been more modern; the use of salvarsan had been thoroughly carried out and the case regarded as clinically cured. As the taking of the Wassermann reaction has been made only during the last year a part of the regular examination routine for our hospital cases, it was made in the case of only a small number of those in whom syphilis was unsuspected. In the case of those in whom the infection was suspected or diagnosed it was regularly made. Notes concerning the Wassermann are given with each case.

I have accordingly divided the forty-one cases into three classes:

(1) cases in which there was a known history of syphilis, with treatment regarded as adequate and resulting in a cure; (2) cases in which the syphilitic infection was recognized as still active, treatment being continued; (3) cases in which a syphilitic history could not be obtained or was specifically denied by the patient, the clinical diagnosis not including syphilis and no antisyphilitic treatment given.

CLASS I.—CASES WITH A HISTORY OF RECOGNIZED SYPHILIS, TREATMENT, AND CLINICAL CURE.

1. CASE C.—Age, sixty-two years. Chancre when a young man; treated by physician; never any other symptoms of the disease; apparent cure. No history of alcoholism. Wassermann not made. Clinical diagnosis of enlarged prostate. Operation. Death.

Pathological Diagnosis. Postoperative infection. Chronic purulent pyelonephritis. Old syphilis. Healed gummata of liver and testis. Orchitis chronica fibrosa syphilitica. Chronic epididymitis. Emphysema. Active syphilis in myocardium and aorta.

2. CASE M.—Age, sixty-three years. "Cured syphilis." No symptoms since chancre when a young man. Clinical diagnosis of peritonitis following operation on bladder. No Wassermann.

Pathological Diagnosis. Postoperative peritonitis. Chronic cystitis. Papilloma of bladder. Chronic prostatitis and vesiculitis. Fatty degeneration of all organs. Bronchopneumonia. Latent syphilis in myocardium, aorta and testes.

3. CASE F.—Age, sixty-four years. No history of infection. Treated with mercury. "Cured." Blood gave a positive, and cerebrospinal fluid a negative Wassermann. Clinical symptoms cardiac. Question of aortic aneurism.

Pathological Diagnosis. Mitral insufficiency and stenosis. Aortic insufficiency. Relative tricuspid insufficiency. Chronic parenchymatous nephritis. General atherosclerosis. Chronic passive congestion of all organs. Healed infarcts in lungs and kidneys. Thrombosis. Latent syphilis of heart and testes.

4. CASE K.—Age, forty-nine years (?). Sudden death following fracture of bones of leg. "Cured" syphilis when a young man. Chronic drinker. No Wassermann. Clinical diagnosis of embolism.

Pathological Diagnosis. Fracture of right tibia and fibula. Thrombosis of veins of right leg. Embolus in left pulmonary artery. Fat embolism of lungs. Early stage of alcoholic cirrhosis. Active syphilis in heart and aorta. Advanced syphilitic fibroid orchitis.

5. CASE S.—Age, forty-five years. Chancre when young. Treated. Later tertiary recurrence. Treatment resumed. "Cured." Drinker. No Wassermann. Committed suicide with carbolic acid.

Pathological Diagnosis. Carbolic acid poisoning. Latent syphilis. Saddle-nose. Gumma of spleen. Active syphilis of heart, aorta, adrenals, and testicles. Advanced orchitis syphilitica fibrosa.

6. CASE M.—Age, seventy years. Syphilis when a young man. "Cured." Chronic drinker. Clinical diagnosis of uremia. No Wassermann.

Pathological Diagnosis. Chronic parenchymatous nephritis. Chronic prostatitis, vesiculitis, pyelitis, and cystitis. Localized chronic leptomeningitis. Coronary sclerosis. Hypernephroma of right kidney. Active syphilis in aorta, myocardium and testicles.

7. CASE R.—Age, fifty-nine years. Date of infection not known. Treated. "Cured." No history of alcoholism. Wassermann negative. No clinical symptoms of syphilis. Clinical diagnosis of tumor of kidney.

Pathological Diagnosis. Hypernephroma of right kidney. Chronic parenchymatous nephritis, prostatitis, vesiculitis, and cystitis. Old tubercles in bronchial nodes. Gummata of spleen and liver. Active syphilis of myocardium, aorta, spleen, liver, and testes.

8. CASE L.—Age (?). Syphilitic infection twenty-three years ago. Treated with mercurials. "Cured." Chronic alcoholism. Died of croupous pneumonia. Both blood and cerebrospinal fluid gave a negative Wassermann.

Pathological Diagnosis. Croupous pneumonia. Syphilitic hepatitis. Syphilis of the aorta, heart, adrenals, and testes.

9. CASE MRS. J.—Age, (?) Time of infection unknown. No clinical signs of syphilis. Blood and cerebrospinal fluid gave negative Wassermann. Diagnosis of nephritis.

Pathological Diagnosis. Chronic parenchymatous nephritis. Syphilitic aortitis. Fibroid heart. Chronic cystitis. Emphysema. Chronic vaginitis.

10. CASE F.—Age, fifty-four years. Chancre at fifteen years of age. Treated. Never any other symptoms. Moderate drinker. Wassermann negative. Carcinoma of rectum.

Pathological Diagnosis. Adenocarcinoma of rectum. Secondaries in pelvis and peritoneum. General cachexia. Amyloid spleen. Syphilitic contracted kidney. Active syphilis of heart, aorta, and testes.

11. CASE G.—Age, forty-five years. Chancre twelve years ago. Treated. "Cured." Wassermann negative. Clinical diagnosis of chronic valvular disease.

Pathological Diagnosis. Aortic insufficiency. Aneurism of ascending aorta. Active syphilitic lesions in heart, aorta, and testes.

CLASS II.—CASES OF CLINICALLY ACTIVE SYPHILIS.

12. CASE W.—Age (?). Date of infection unknown. Blood and spinal fluid gave positive Wassermann. Under treatment for syphilis of central nervous system. Died of pneumonia.

Pathological Diagnosis. Acute purulent bronchopneumonia. Active syphilitic aortitis and meningoencephalitis. Fatty liver and heart. General marasmus.

13. CASE T.—Age, forty-seven years. Denied syphilitic infection. Symptoms of tabes. No history of alcoholism. No Wassermann. Under antisyphilitic treatment.

Pathological Diagnosis. Aictve syphilitic leptomeningitis. Miliary gummata in cord and brain. Diffuse degeneration and sclerosis of cord and brain. Chronic parenchymatous nephritis. Active syphilitic lesions in heart and aorta. Orchitis syphilitica fibrosa.

14. CASE H.—Age, forty-four years. Physician. Accidental infection nine years previously. Blood and spinal fluid gave positive Wassermann. Under active treatment. Early stage of paresis.

Pathological Diagnosis. Syphilis. Paresis. Acute purulent pneumonia. Subacute parenchymatous nephritis. Acute purulent pyelitis. Chronic cystitis. General atherosclerosis. Active syphilitic lesions in brain, cord, heart, aorta, liver, adrenals, and testicles.

15. CASE W.—Age, forty-four years. Had hard chancre when twenty-one years old. Secondaries. Treated. Now shows early stage of tabes. Wassermann positive. Under active treatment.

Pathological Diagnosis. Syphilis. Tabes. Active syphilitic lesions in brain, cord, heart, aorta, liver, and testicles. Acute parenchymatous nephritis. Chronic cystitis, vesiculitis, and prostatitis. Healed tuberculosis of bronchial nodes.

16. CASE S.—Age, forty-five years. Chancre fourteen years ago. Now symptoms of tabes. Wassermann positive. Salvarsan by intraspinal injections. Arsenical poisoning.

Pathological Diagnosis. Syphilis of brain, cord, heart, aorta, pancreas, and testes. Chronic interstitial nephritis.

CLASS III.—SYPHILIS DENIED OR NOT SUSPECTED CLINICALLY.

17. CASE G.—Age, sixty-three years. Denied venereal disease. No history of symptoms of syphilis. No Wassermann. No alcoholism. Clinical diagnosis of prostatic enlargement. Operation.

Pathological Diagnosis. Croupous pneumonia. Early stage of meningitis. Hypertrophy and dilatation of heart. Arteriosclerosis. Chronic parenchymatous nephritis and pyelitis. Chronic cystitis and prostatitis. Syphilitic lesions in heart, aorta, and testes.

18. CASE D.—Age, sixty years. No history of syphilis. No Wassermann. Clinical diagnosis cancer of stomach.

Pathological Diagnosis. Colloid carcinoma of pylorus. Chronic parenchymatous nephritis. Arteriosclerosis. Syphilitic lesions in heart, aorta, adrenals, and testes.

19. CASE MRS. C.—Age, forty-five years. No history of syphilis. No Wassermann. Clinical diagnosis cystadenoma of ovary.

Pathological Diagnosis. Cystadenocarcinoma of ovary. Metastases in liver, spleen, and regional lymph nodes. Syphilitic lesions in heart and pancreas.

20. CASE CO.—Age, forty-three years. No history of syphilis or alcoholism. No Wassermann. Clinical diagnosis of tumor of intestines.

Pathological Diagnosis. Primary lymphosarcoma of intestine. Secondaries in mesenteric and retroperitoneal lymph nodes, kidney, and liver. Chronic parenchymatous nephritis. Fatty cirrhosis of liver. Syphilis of heart, aorta, pancreas and testes.

21. CASE S.—Age, sixty-eight years. No history of syphilis. No Wassermann. No history of alcoholism. Clinical diagnosis of carcinoma of stomach and senility.

Pathological Diagnosis. Active syphilis of brain, cord, heart, aorta, and testes. Early stage of paresis and tabes. Chronic prostatitis. Chronic parenchymatous nephritis.

22. CASE MRS. S.—No history of syphilis. No Wassermann. Dementia.

Pathological Diagnosis. Bronchopneumonia. Syphilis of heart and aorta. Coronary sclerosis. Fibroid heart. Biliary calculi. Adenomatous polyp of uterus.

23. CASE Y.—Age, sixty-six years. Syphilis denied. No history of symptoms. No alcoholism. No Wassermann. Clinical diagnosis of myocardial insufficiency and coronary sclerosis.

Pathological Diagnosis. Active syphilitic myocarditis with cardiac thrombosis. Syphilitic aortitis. Multiple infarction of lungs and kidneys. Chronic parenchymatous nephritis. Early stage of cirrhosis of liver. Syphilitic lesions in adrenals and testicles. Chronic prostatitis, cystitis, vesiculitis, and pyelitis.

24. CASE MRS. WA.—Age (?). Doubtful history of syphilis. Never pregnant. Negative Wassermann. Clinical diagnosis of carcinoma of uterus. Death after operation.

Pathological Diagnosis. Carcinoma of uterus. Recurrence. Postoperative sepsis. Acute parenchymatous nephritis. Syphilitic lesions in heart and liver. Glissonian cirrhosis.

25. CASE MRS. B.—Age, twenty-four years. Treated by previous physician for syphilis. Syphilis excluded in hospital examination. Wassermann negative. Clinical diagnosis of chronic valvular lesions.

Pathological Diagnosis. Active late syphilis. Chronic syphilitic myocarditis and aortitis. Combined stenosis and insufficiency of mitral, aortic, and tricuspid valves. Subacute parenchymatous

nephritis. Multiple infarcts of lungs and kidneys. Severe anemia. Fatty liver. Syphilitic ulcer of leg. Gangrenous stomatitis, syphilitic with secondary infection. Colloid goitre.

26. CASE M.—Age, fifty years. No history of syphilis. Negative Wassermann. Clinical diagnosis of thoracic aneurysm and carcinoma of stomach.

Pathological Diagnosis. Carcinoma of stomach. Syphilitic lesions in heart, aorta, and testes.

27. CASE K.—Age (?). Denied venereal disease. Moderate drinker. Negative Wassermann. Enlarged prostate.

Pathological Diagnosis. Medullary carcinoma of prostate. Generalized metastasis. Addison's disease. Hydrothorax. Syphilis of heart, aorta and testes. Subacute parenchymatous nephritis. Chronic catarrhal gastritis. Hydrocele.

28. CASE MC.—Age, forty-four years. No history. Entered in toxic state. Suspected arsenical poisoning. No Wassermann.

Pathological Diagnosis. Acute alcoholic intoxication. Chronic alcoholism. Early stage of fatty cirrhosis of liver. Chronic parenchymatous nephritis. General atherosclerosis. Chronic pachymeningitis. Syphilis of testes.

29. CASE G.—Age, thirty years. Denied venereal disease. Negative Wassermann. Moderate drinker. Clinical diagnosis of chloroma.

Pathological Diagnosis. Primary carcinoma of pancreas; metastases in vertebræ, retroperitoneal glands, mesentery, adrenals, testes, and bronchial nodes. Syphilis of testes.

30. CASE MRS. B.—Age (?). No history or symptoms of syphilis. Wassermann negative on blood, 4+ positive on spinal fluid. Eight months pregnant. Clinical diagnosis of tuberculous meningitis. Miscarriage. Dead fetus.

Pathological Diagnosis. Lobar pneumonia. Chronic tuberculosis of bronchial nodes. Miliary tuberculosis of lungs, liver, spleen, and peritoneum. Caseation of one adrenal. Syphilis of myocardium and of fetal chorion.

31. CASE B.—Age, forty-two years. Gonorrhea at twenty years of age. Denied syphilis. Wassermann negative. Drinker. Clinical diagnosis of alcoholic cirrhosis.

Pathological Diagnosis. Alcoholic cirrhosis. Syphilis of heart, aorta, and testes.

32. CASE W.—Age, seventy-eight years. No history of syphilis. Wassermann positive. No clinical diagnosis.

Pathological Diagnosis. Syphilis of heart, aorta, pancreas, and testes. Syphilitic peribronchitis. Chronic parenchymatous nephritis. General marasmus.

33. CASE B.—Age, forty-eight years. No history of venereal diseases. Wassermann negative. Clinical diagnosis of prostatic enlargement and uremia.

Pathological Diagnosis. Primary carcinoma of prostate. Metastases in liver. Chronic cystitis, ureteritis, and pyelonephritis. Syphilis of heart, aorta, and testes. Fatty liver and adrenals. Pulmonary edema. General atrophy. Emphysema. Infected cystotomy wound.

34. CASE A.—Age (?). No history of syphilis. No Wassermann. Clinical diagnosis of diabetes. Mitral insufficiency.

Pathological Diagnosis. Diabetes. Atrophy of pancreas. Dilatation of heart. Purulent bronchopneumonia. Subacute parenchymatous nephritis. Syphilitic orchitis.

35. CASE AR.—Age, forty-eight years. No history of syphilis. Wassermann negative. Diagnosis of diabetes. Sepsis.

Pathological Diagnosis. Diabetes. Infected squamous-cell carcinoma of finger. Ascending purulent lymphangitis of right arm. Septicemia. Syphilis of heart, aorta, pancreas, and testes.

36. CASE AL.—Age, sixty-nine years. Denied venereal disease. Wife had one miscarriage. Drinker. Wassermann not taken. Diagnosis of croupous pneumonia and pernicious anemia.

Pathological Diagnosis. Croupous pneumonia. Syphilis of heart, aorta, and testes. Syphilitic contracted kidney. Anemia gravis. General atrophy.

37. CASE MRS. BO.—Age, forty-four years. No history of syphilis. Never pregnant; no precautions taken. Wassermann negative. Died of general peritonitis.

Pathological Diagnosis. Acute purulent peritonitis. Infected laparotomy wound, posthysterectomy. Syphilis of heart and adrenals.

38. CASE W.—Age, fifty-five years. Denies venereal disease. Moderate drinker. One Wassermann test negative, second one positive. Diagnosis of alcoholic cirrhosis.

Pathological Diagnosis. Alcoholic cirrhosis. Ascites. Portal stasis. Syphilis of heart, aorta, and testes. Emphysema. Chronic prostatitis.

39. CASE J.—Age, seventy-two years. Denies venereal disease. Moderate drinker. Wassermann negative. Clinical diagnosis of myocardial insufficiency.

Pathological Diagnosis. Aortic insufficiency and stenosis. Sclerosis of endocardium. Mitral stenosis and insufficiency. Cardiac hypertrophy and dilatation. Syphilis of heart, aorta, pancreas, and testes. Syphilitic ulcer of leg. Emphysema. Brown induration of lung with multiple infarcts. Early interstitial nephritis. Early stage of alcoholic cirrhosis. General atrophy.

40. CASE C.—Age, fifty-nine years. Denied venereal disease. No Wassermann. Clinical diagnosis arthritis deformans of spine. Terminal pneumonia. Pyelonephritis.

Pathological Diagnosis. Primary scirrhous adenocarcinoma of prostate with metastases in vertebræ, ribs, pelvic bones, lungs,

liver, and retroperitoneal lymph nodes. Aspiration purulent bronchopneumonia with abscesses of lung. Multiple abscesses in kidneys. Chronic cystitis. Syphilis of heart, aorta, adrenals, and testes.

41. Case Ca.—Age, forty-five years. Denied venereal disease. One Wassermann test negative; second one positive.

Pathological Diagnosis. Croupous pneumonia. Chronic ulcerative colitis with multiple polyp formation. Chronic dysentery. Amyloid spleen. Syphilis of heart.

It will be seen from the above list that there are 11 cases with clinical diagnosis of recognized and treated syphilis regarded clinically as cured, 5 cases of active syphilis under treatment for symptoms of the disease, and 25 cases in which a diagnosis of syphilitic infection was excluded clinically because of absence of symptoms and denial of previous infection. It is very probable that some, if not the majority, of the patients in this third group were actually in total ignorance of any specific infection. In the case of the women it is practically certain that this was the case. There can be no doubt that many people acquire syphilis without recognizing any of the earlier stages, either through ignorance of these or because the early symptoms are slight or entirely absent. Some of the male patients in this group no doubt had had the primary sore so long before that they had either forgotten it or no longer attached any importance to it. Having long ago accepted that condition as cured, they consider it as past history and deny that it ever took place. It is, of course, a very common experience in dealing with patients of this type to receive repeated denials of the occurrence of syphilitic infection, and the information of such an infection must be drawn out by special and prolonged tactics of questioning. It is also possible that a number of these cases were congenital infections, and unrecognized by the patients. Particularly in the case of women may congenital syphilis run an unrecognized latent course throughout the patient's lifetime.

In all of these 41 patients the lesions of active syphilis were practically of the same nature, whether in cases that had been treated, or were being actively treated, or had received no treatment at all. Active syphilitic lesions were found in the heart in 36 cases, in the aorta in 32, in the testes in 31, in the liver in 4, in the adrenals in 6, in the spleen in 1 case, pancreas in 6 cases, and central nervous system in 5 cases. As five of the patients were women, and deducting these, the lesions in the testes occur as frequently as those in the heart. The organs most frequently the seat of active lesions in order of frequency of occurrence would be aorta, heart, testes, adrenals, pancreas, central nervous system, liver, and spleen. It is also of great interest to note that in these cases there were 16 cases of subacute or chronic parenchymatous

nephritis; 2 of acute parenchymatous and 5 cases of interstitial nephritis, although no relationship between the syphilis and the kidney lesions can be positively affirmed. It is very probable that the central nervous system would show a much greater rate of involvement had this been regularly examined, but in the majority of these cases an examination of cord and brain was not permitted. In all five of the active cases of Class II the central nervous system was examined and showed marked syphilitic lesions.

In the determination of the existence of syphilitic infection in any given case coming to autopsy the heart, aorta, and testis in the male are the organs that should receive the most thorough examination. If the latent syphilis is present, active lesions will be found in one or the other of these organs if they occur anywhere within the body. The triad of interstitial myocarditis, aortitis, and orchitis fibrosa may be taken as a pathological complex indicating the occurrence of a syphilitic infection in the male. In medicolegal work these three organs should be chosen in preference to all others for microscopic examination when the question of syphilis is concerned. In the case of the female, the heart and aorta, pancreas and adrenals should be examined for evidences of latent syphilis, and the lesions in these organs are, as a rule, less marked than in the male body.

The number of spirochetes in old latent syphilis is usually small; only in a few cases have they been found in numbers at all approaching those of early congenital or acquired syphilis. They lie in small groups or colonies in small perivascular infiltrations; usually outside of the walls of small veins. This is particularly true in the case of the aorta, where the organisms are never found in the intimal side of the vessel, but are found colonized in the outer portion of the media, or, most frequently of all, in the adventitia around the veins of the vasa vasorum. In the heart muscle they are found in small areas of connective-tissue proliferation and infiltration around the smallest branches of the coronary vessels, particularly the veins, and in similar areas in the muscle. The amount of inflammatory infiltration may be very slight. The pancreas in every case of latent syphilis shows more or less pronounced increase of stroma, areas of intralobular pancreatitis, atrophy, and perivascular infiltrations. The syphilitic nature of all these changes has not yet been determined. Only in one of the diabetic cases have spirochetes been demonstrated in the pancreatic lesions. It is of interest to state here that six autopsy cases of diabetes occurring in our service since 1907 have all shown histological changes of syphilis, and in four of these cases spirochetes have been demonstrated in the myocardium. The adrenal lesions consist of mononuclear infiltrations in the medullary portion or at the boundary between cortex and medulla, around the veins, and also thickening of the corpuscle. Spirochetes have been demon-

strated in the infiltrated areas. The lesions of the testes consist of vacuolation and disappearance of the germinal cells, hyaline thickening of the basement membrane of the tubules with gradual obliteration of the seminiferous tubules, the so-called orchitis fibrosa syphilitica chronica. A state of fibroblastic proliferation precedes the hyaline change, and spirochetes are found in the basement membrane in this early state. Small collections of mononuclear cells may be found between the tubules in the neighborhood of small vessels. Spirochetes may be found in these areas also. The close relationship of the spirochete to the seminiferous tubules makes the entrance of the organism into the tubule a very probable occurrence, and can be taken as a very strong argument for the possibility of seminal infection. In congenital syphilis and in early acquired syphilis I have found the testes swarming with spirochetes even when no histological changes can be recognized in the organ. In such cases great numbers of spirochetes must gain entrance to the tubules and pass out with the semen. The difficulties in proving this are, of course, very obvious.

I have taken as a criterion for diagnosis only morphologically typical spirochetes, and have based my findings only upon the demonstration of those showing characteristic quality and morphology. In addition to typical organisms, we find in the old latent cases especially irregular and atypical forms (beaded forms, straight forms, fragmented forms, thicker or thinner spirals, etc.) in the colonies with the typical forms. I believe these to be involution forms, but am not yet prepared to make positive statements concerning this point. This point is now being investigated. The beaded and fragmented forms may in part be postmortem changes, since they can be produced in spirochetes in syphilitic tissues left in the cold or warm room for some hours after removal from the body before the formol-fixation. Experiments with liver, spleen, and lungs of congenital syphilis containing innumerable spirochetes show that similar changes in the spirochetes can be produced by the conditions mentioned above. Taking the typical spirochetes as our criterion, there can be no question of any confusion with fibrillæ of reticulum, elastic tissue, etc. The latter, even when heavily precipitated with silver, never resemble the spirochete in morphology or quality to such an extent as to make confusion of identity possible.

Our autopsy material comes almost wholly from the University Hospital, a State hospital whose patients represent the average middle-class population of the State. It is important to note the prominent incidence of latent syphilis in this class, about one-third of the adult autopsies. Still more important is the fact, already mentioned, that the greater part of these latent cases give no clinical history of syphilis, and are in ignorance that they have acquired the disease. They entered the hospital for other conditions, most

prominent of which are cardiovascular-renal symptoms and conditions. Only the autopsy reveals that they are spirochete carriers and have a latent infection of very low virulence, which in all of the cases must be very old, and not recent, because of the fibroid character of the lesions. Most of the lesions found represent healed syphilitic areas; but in all cases active areas of inflammation are still present, and can always be found after a search more or less prolonged, as the case may be. The same histological changes, often of the same degree and extent, occur in the heart, aorta, pancreas, and testes of all cases of syphilis, treated, "cured," untreated, and unsuspected.

The sociological importance of this is very great. It places latent syphilis upon a plane of importance nearly, if not equalling, that of tuberculosis, as a factor opposed to the health and progress of the race. Latent syphilis, I believe, will be found to be the chief factor in the production of myocardial insufficiency and the cardiovascular-renal complex, apparently so rapidly increasing.

My pathological experience makes me believe that the heart and aorta of every latent syphilitic are involved in the infection. From the stand-point of life insurance, latent syphilis becomes a medical and sociological factor of the greatest importance. The spirochete carrier is a bad risk. He is also a possible source of danger through infection to those with whom he lives in most intimate contact. In these old latent cases seminal transmission is probably the most dangerous possibility to be considered.

The question of a possible reinfection has been suggested in explanation of some of these cases. No clinical evidence, of a second infection, of course, exists in any one of these cases; and in most there is no history of the first infection. I think such a possibility very improbable. I, myself, have never seen a true reinfection, and regard the relatively few cases described in the literature as not above suspicion. Sores in all respects resembling the hard chancre may appear upon the genitals or other portions of the body in late active and treated cases of syphilis. Even on microscopic examination they cannot be distinguished from the primary chancre. A primary sore may also be made to disappear early by the use of preventive or curative mercurial ointments or by one or two injections of salvarsan; but it may return after a few weeks or months. I have seen several cases in which such a recurrence of the chancre took place six months after the primary sore had disappeared under such treatment, and without chance for reinfection. In one case recurrence took place one year later. Had opportunities for reinfection been present, such recurrent primaries might easily be regarded wrongly as reinfections.

I believe that many of these latent cases without history are innocent congenital cases or are the victims of familial infection. Congenital syphilis, in the female, and in the third generation has

an especial tendency to run a mild latent course, sometimes without any clinical sign or symptom. It may not be recognizable at all during life. The same thing is sometimes true of certain familial infections; certain members of the infected family may show absolutely no clinical signs or symptoms, except perhaps a positive Wassermann. This may also be negative. In other cases obscure signs of the disease (ocular alone) may be the only evidence found of the infection. The sociological and medical problems associated with congenital syphilis are very great, and we are just beginning to appreciate them.

As to the Wassermann reaction in latent syphilis a certain percentage of cases will give a positive reaction, but many will be found to have a negative reaction. Blood and spinal fluid will often give contradictory results. Under given conditions only strongly positive reactions have any positive diagnostic value; the negative Wassermann cannot be taken as any evidence of the absence of latent syphilis.

The apparent symbiosis of spirochetes within such organs as the heart, aorta, and testes through a period of many years without causing greater damage or giving rise to more marked symptoms must be taken as proof that the organisms have a very low virulence in such cases. "Cured" syphilis in many cases, if not all, is but a latent infection or "symbiosis," with spirochetes that have a very low virulence, in some cases not much greater than that of the intestinal flora. It becomes increasingly important to know the conditions under which organisms remaining so relatively inactive over long periods of time may at times renew their aggressiveness and cause more marked damage.

The general hygiene of the spirochete carrier is probably of as great importance as the general hygiene of latent tuberculosis. This is a point not yet sufficiently emphasized in the treatment of syphilis.

The therapeutic lesson is evident. Promises of cure within definite time-limits can never be safely made, and our advice as to treatment must include the possibility of treatment extended over many years. The syphilitic must be treated as a germ carrier. The latency of the infection seems to be the same in many untreated cases as in those receiving very good treatment. Our present-day treatment seems only to succeed in rendering the infection latent rather than in curing it. Clinical cures may not be cures at all, as shown by the autopsy. From the stand-point of eugenics it may also be said that absence of symptoms, or even of history of infection, and negative Wassermann reaction cannot be taken as an absolute criterion of freedom from latent syphilis.

HEREDITARY SYPHILIS IN THE LIGHT OF RECENT CLINICAL STUDIES.[1]

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Transmission. Whatever may have been the real position of Paracelsus—whether a great physician out of touch with his times or a master quack—we must credit him with being the first to assert the existence of an inherited form of syphilis. This was in the year 1529, a short time after the introduction of the disease into Europe from the West Indies; but a general belief in the transmission of syphilis from parents to offspring did not prevail until the latter part of the seventeenth and eighteenth centuries, although an infantile form of syphilis was well recognized. With the acceptance of the general idea there has been a century-long controversy in regard to the details of the method of transmission, which, expressed in its simplest form, has centered about the question of whether or not syphilis in the father can be transmitted to the child *in utero* without the mother at the same time becoming infected.

Without going into the historical details of the years of controversy, we can briefly sum up the position taken by the two most prominent groups of syphilographers. One group has held to the view of germinal transmission, which to a large extent is based upon the observations that:

1. In most cases of inherited syphilis the father is admittedly syphilitic.
2. That many women without clinical signs or history of lues bear syphilitic children to a syphilitic father.
3. That the treatment of a syphilitic father in many instances has lead to the mother bearing normal children after having previously given birth to a syphilitic child.
4. That instances are known of where an untreated woman has borne syphilitic children to a syphilitic father and subsequently normal children to a normal father.

The last two observations do not always hold true and the question at issue really involves the second observation—that is, of healthy mothers giving birth to syphilitic children. It is admitted that in many cases the mother is syphilitic, being anteconceptionally, conceptionally, or postconceptionally infected.

In 1837 Colles published the observation that apparently normal

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women bearing syphilitic children acquire an immunity to syphilis, or, more correctly, do not contract syphilis when exposed to infection. This has been interpreted in two ways: (1) as an expression of a passive immunity due to the absorption of immune bodies from the syphilitic fetus through the placenta, and (2) as the result of an active immunity, the woman having syphilis. According to the ideas of those who believe that in all cases the mother is infected, it is only the negative Colles' mothers—that is, the few reported cases in which the mothers of syphilitic children have subsequently become infected with syphilis—which lend any valid support to the theory of the possibility of a purely paternal infection, and the accuracy and correctness of the clinical observation has been questioned in these cases. The second group, as we have said in discussing the first, holds to the view that the mother is always infected, and that without maternal syphilis there is no syphilis of the offspring.

This controversy, which lasted for so many years, was based upon the interpretation of clinical observation, and in brief depends upon whether or not germinal infection is possible—that is, whether the spermatozoön can carry the infection and the offspring become syphilitic without the mother acquiring the disease. Within the last decade—for it was in 1906 that Schaudinn's first paper appeared—our knowledge of syphilis has increased more than in the entire period of time elapsing since its recognition in the latter part of the fifteenth century, and the discovery of the etiological organism and of serodiagnostic methods have helped to clarify in many ways the questions which have confused this subject of inherited transmission.

The Treponema pallida of Schaudinn is an organism some 6 to 15 microns in length and with some 10 to 26 undulations. The head of a spermatozoön—which is the only portion capable of carrying an organism within it—is from 3 to 5 microns in length. Hence, the physical impossibility of the treponema being carried in the spermatozoön, which is essential if we are to have a true germinal transmission, unless the organism undergoes some morphological change in its life history with which we are at present unfamiliar and have no reason to suspect. Moreover, we know of no example of germ-cell transmission of an infectious disease in human or veterinary pathology. With everything thus against the possibility of such a method of transmission the burden of proof is with those who advance the theory, and as yet no evidence has been submitted in support of their position.

Although, in all probability, germinal transmission does not occur, as we have seen, it has been found that the seminal fluid can carry the infection, and the testicles are recognized as a not infrequent seat of latent syphilis. Finger was able to transmit an infection to two of the higher apes with seminal fluid from florid

lues, and Neisser has transmitted the infection by transplanting the testicles of syphilitic apes. It has not been possible to demonstrate the presence of spirochetes in seminal fluid by microscopic methods. These experiments, it must be kept in mind, only prove the infectiousness of seminal fluid from active syphilitics, and do not bear a direct relation to the question of paternal transmission in hereditary syphilis.

Turning now to the question of women bearing syphilitic children who show no signs of syphilis: There are two possibilities—either the women are not syphilitic, or else they have syphilis in an inactive or latent form. With the development of serological methods for the diagnosis of syphilis, their applicability to this question was at once recognized and many small series of tests were soon reported. In these small series the percentage of positive reactions in the blood of mothers of syphilitic children ran from 40 to 60.

In a recent study of familial syphilis made in our clinic in St. Louis we had occasion to test the blood of 85 mothers of syphilitic children. Of these 85 mothers, 74, or 87 per cent., denied all knowledge of infection, nor was there anything in the history given us that would indicate a syphilitic infection outside of a history of frequent abortions. Dr. Jeans[2] has recently collected these cases and found that the blood of 73 of the 85 gave a positive Wassermann test. Of the remaining 6 all but one were tested after an interval of at least ten years had elapsed between the birth of the last syphilitic child and the time of the test. In the one exception the interval had been four years. In some of these cases a healthy child had been born during this period.

In this way, by means of the complement-deviation test, it has been found presumable that these apparently healthy mothers are immune, in Colles' sense, because they have syphilis in a latent form. Hochsinger, in order to uphold his older ideas, would have us believe that in these cases the positive reaction was an indication of immunity rather than of infection. This interpretation is incorrect, as a positive Wassermann indicates tissue response against superinfection due to the presence of the spirochetes rather than a true reaction of immunity. As long as the reaction remains positive a superinfection never occurs, but it is well known that when treatment has been pushed to a point where it has become persistently negative, a second "primary" infection has occurred in many cases. Thus we do not have an immunity in syphilis in the true sense of the term, and a positive Wassermann signifies infection. Hence, we must regard it as evidence of or a symptom of syphilis whether the infection is active or latent, as in the cases under discussion.

In the present state of our knowledge we can summarize the

[2] Familial Syphilis, Am. Jour. Dis. Child., 1916, xi, 11.

evidence as pointing to the view that in hereditary syphilis the mother is always infected, although very frequently the infection is latent and that true germinal infection does not occur.

SYPHILIS AS A SOCIAL PROBLEM. No accurate figures are available as to the incidence of hereditary syphilis. The disease is not reportable, and even if it were it is doubtful if the records obtained in this way would be of any value, as the condition is frequently overlooked, and when recognized would be concealed in many cases because of the stigmata attached. With improved methods of diagnosis we are beginning to learn that it is far more common than previously thought, as many conditions in which the etiology was obscure have been found to be the result of a syphilitic infection. Hospital statistics are of little value in this connection. In St. Louis we have been particularly interested in hereditary syphilis, and have admitted many cases to the Children's Hospital for study which would normally have been cared for in the out-patient clinic, and hence the proportion of syphilis to the total number of admissions is relatively high. We have seen between 300 and 350 children with an hereditary infection in three and a half years and have undoubtedly failed to recognize a number of cases. We have also found many cases of latent syphilis by testing the apparently healthy children of syphilitic families. What is more important is the number of obscure clinical conditions which have been found to be syphilitic in origin.

The importance and cost of syphilis to the family and the community is not generally appreciated. About this point we have collected some interesting information: For a period of about a year an attempt was made to obtain extensive data in regard to the family of every syphilitic child coming to the clinic, to examine all of the other living children as well as the parents, and to test the blood of each member by the complement-deviation method. In this way data was assembled for 100 syphilitic families. Many marriages (10 to 30 per cent.) remain sterile as a result of syphilis and others (13 per cent. according to Haskell) result only in abortions. Our material includes only those families in which a living child came under our direct observation and care.

In these 100 syphilitic families 331 pregnancies occurred which resulted as follows:

Abortions	100 or 30.2	per cent.
Stillbirths	31 or 9.3	"
Living births	200 or 60.5	"

Thus 40 per cent. of the pregnancies terminated in the death of the fetus before term. If the parents had been healthy and of the same social strata we might have expected 30 to 35 deaths before term, or a mortality of 10 per cent. instead of 40 per cent.

Considering next the 200 living births: At the time the data were collected 39 were dead and 161 alive, but 12 of the 161 died

during the course of the investigation. Of the 161 examined 107 had both clinical signs of syphilis and a positive Wassermann; 5 were clinically positive but gave negative tests (in all of these the family gave a history of syphilis); 16, although negative as regards clinical manifestations, gave positive reactions, and therefore belong to the group of latent syphilitics. Thus but 33 of the 161 living children were free from the infection, and if we attribute the deaths occurring before term to syphilis, we find that of the 331 pregnancies in 100 syphilitic families but 10 per cent. escaped the infection. The toll is summarized in the following table:

331 PREGNANCIES IN 100 SYPHILITIC FAMILIES.

131 or 40 per cent. died before term 51 or 15 per cent. died after birth	55 per cent. dead
116 or 35 per cent. living but syphilitic	35 per cent. syphilitic
33 or 10 per cent. living and free from syphilis	10 per cent. escaped
331	

If we add to this record and take into consideration the physical condition of the parents—both of whom were syphilitic in almost all of our cases—we begin to grasp the appalling importance of syphilis from a social standpoint.

In order to show this in another way, studies[3] were made in our clinic in which the waste (total deaths to total pregnancies) occurring in 100 families in which we were treating children with contagious disease, and in 100 families selected at random from our records, were contrasted with the waste in 100 syphilitic families. These groups are designated as C. R. and S. respectively and the data briefly summarized in the following table:

Group.	Total pregnancies.	Deaths before birth.	Born living now dead.	Total.	Per cent. waste.
C.	444	46	70	116	26
R.	442	42	59	101	22
S.	453	116	104	220	48

The increase in the waste for the syphilitic group of 100 per cent. does not represent the total waste, as it is fair to assume that three-quarters of the living children are syphilitic and many of these defective.

There are many things of interest in connection with the question of family syphilis—the way in which the infection seems to die out, the apparent tendency to involvement of the nervous system in some families, for example, which cannot be discussed in the limits of this paper. The question of the transmission to the third generation, about which so much has been written by Fournier, requires mention in passing. In the light of recent discoveries this entire chapter must be rewritten, as definite tests can now be applied

[3] Jeans and Butler, Hereditary Syphilis as a Social Problem, Am. Jour. Dis. Child., 1914, viii, 327.

when before we had to rely upon clinical observation which was questionable in many of the cases quoted as examples of this form of transmission. Today, in order to prove existence of an infection being transmitted to the third generation, we must not only have a positive Wassermann test in the child, its mother, and its maternal grandmother, but also in the brothers and sisters of the mother. This is essential to exclude faulty observation, and cases fulfilling these conditions must be adduced before we can state definitely that transmission to a third generation occurs. We have no cases fulfilling these conditions in our records, although in some cases there is a strong clinical suggestion of such a mode of transmission. We recently had in the hospital the child of a mother with inherited syphilis. The child was mentally and physically defective, but was free from a true specific infection. This is probably the form in which hereditary syphilis shows itself most frequently in the third generation, but these children are not syphilitic in the sense of true inherited transmission.

Clinical Manifestations. Passing now to a consideration of some points in regard to the clinical manifestations of hereditary syphilis.

From a clinical standpoint we have found it of service to divide our cases of inherited syphilis into four groups:

1. Fetal.
2. Infantile.
3. Late or tardy.
4. Latent.

In the first group, under the term fetal syphilis, we include the cases in which manifest signs of lues develop *in utero*. Thus, stillborn as well as living infants are included. It is this form of syphilis which the obstetrician sees in his practice and the death rate is extremely high for the infants born alive. In the second group, infantile hereditary syphilis, are placed the cases which develop clinical lesions after birth and during the first year of life, and in the third group, "late" syphilis, those cases developing symptoms after the first year regardless of whether or not there have been previous symptoms during infancy. The last (fourth) group is made up of apparently normal children whose blood gives a positive Wassermann reaction. This group, as a rule, goes unrecognized unless some other member of the family shows clinical signs of syphilis and thus furnishes a reason for a blood test being made. That these cases are not uncommon is shown by the number of children developing "tardy" lesions with a negative history as regards clinical manifestations during infancy. While the "infantile" lesions have doubtlessly been overlooked in some of these patients with "late" lesions, this can hardly be the case with all. In the series reported above there were 16 latent cases among the 116 living syphilitic children in the 100 families.

One of the most striking things about the clinical manifestations

of hereditary syphilis is the distinctive and almost uniform character which the lesions show in the infantile group and the varied and bizarre ways in which the syphilitic infection appears in the late cases. This has been compared with the secondary and tertiary manifestations of acquired syphilis, and in general the comparison is good, although not strictly accurate. There is no distinctive primary lesion in inherited syphilis in the sense the term is used in the acquired form, as the infection takes place through the blood. As will be shown below there is a certain period of latency or incubation time between the time the infection takes place *in utero* and the development of visible symptoms after birth, which in a way corresponds to the time elapsing between the appearance of the chancre and the secondary lesions in acquired syphilis. There is no satisfactory explanation of why syphilis develops in such diverse ways. It would seem probable that whether fetal or infantile syphilis develops in a given case depends upon the time infection takes place *in utero*, infection early in pregnancy leading to early death and abortion, and infection occurring late to the infantile cases. Between these two may be innumerable gradations.

As the infantile and tardy groups are the most important I wish to discuss these in more detail. I have recently, together with Dr. Jeans,[4] studied the records of 100 consecutive cases of the infantile type, and, unless otherwise stated, the figures given below refer to this series. Where the totals are under 100 for any given point it means that the data regarding the point under consideration were unsatisfactory in the number of cases omitted.

As a rule, the first clinical symptoms of the infantile group develop in the first two months of life (81 per cent.), and the majority of these in the first month. In the accompanying table the time of development of the earliest symptom is shown for 95 cases:

Time of appearance.	Cutaneous eruptions.	Rhinitis.	Epiphysitis.	Wasting and Wassermann.	Jaundice.	Hemorrhage and edema.	Total.	
1 week	4	12	..	..	..	.....	16	
2 weeks	2	3	..	..	..	.....	5	Total in first month, 51
3 weeks	3	6	5	..	..	.....	14	
4 weeks	7	6	2	..	..	1	16	
5 weeks	..	1	1	..	..	.....	2	
6 weeks	6	7	..	..	..	.....	13	Total in second month, 30
7 weeks	2	3	..	..	..	.....	5	
8 weeks	6	1	1	1	1	.....	10	
3 months	5	1	..	..	..	.....	6	
4 months	1	1	..	3	..	Iritis 1	6	
6 months	1	..	..	..	..	.....	1	
10 months	1	..	..	..	..	.....	1	
Total	38	41	9	4	1	2	95	

[4] Observations on Infantile Syphilis, Am. Jour. Dis. Child., 1916, xi, 177.

In the majority of the infants developing lesions early a rhinitis or coryza was first noted, but in the entire group the number of cases in which a rash was noted first is about the same. The most striking thing about these cases is that so many do not develop lesions until so long after birth, although infection takes place *in utero*. Two explanations are possible: one is that the infection varies both quantitatively and qualitatively in different cases—that is in one few organisms and in another many may gain entrance—or that the organisms may vary considerably in their virulence. With these variables any number of gradations are possible. A very plausible explanation, suggested by Rietschel, is that in these infantile cases the fetus is not infected until near the end of the pregnancy, when the beginning uterine contractions, which may precede parturition by a number of days, open a portal of entrance for infection by breaking loose the placental villæ and tearing open the sinuses, in this way opening a direct route for the transmission of the spirochetes. After a more or less definite period of time clinical signs of the infection appear, and the length of this time after parturition is dependent upon the time previous to parturition at which infection takes place. There are a number of obvious objections to this being more than a partial explanation.

It is a common statement that syphilis in an infant shows itself in two ways: either by producing a general dystrophic condition or by the appearance of more or less specific lesions. As a matter of fact, the two are usually combined and the first occurs but rarely as an entity. It was formerly supposed that many of the various congenital malformations had a luetic basis, but it has been shown by the Wassermann test that there is no relationship between the two more than that of a chance association. Thus, Holt[5] did not find a single syphilitic infection among 56 consecutive infants with congenital malformations (spina bifida, congenital heart disease, hare-lip, etc.), and in our experience it is not a common occurrence, although we have found the two occasionally associated. On the other hand, Browning[6] obtained 17 positive reactions in 20 patients with congenital heart disease, and Findlay,[7] of Glasgow, in 7 of 11 patients. In the parents of 2 of the 4 negatively reacting cases the reaction was positive. Naturally, I am inclined to trust our own experience and doubt very much if there is any etiological relationship between inherited syphilis and congenital malformations.

As intimated above the specific infection exerts a harmful influence upon the nutrition of the infant much greater than that which

[5] Wassermann Reaction in Hereditary Syphilis, etc., Am. Jour. Dis. Child., 1913, vi, 166.

[6] Syphilis and the Health of the Community, British Med. Jour., 1914, i, 77.

[7] Hereditary Syphilis, Glasgow Med. Jour., 1914, lxxxii, 401.

accompanies any type of chronic or acute infection, and this, no doubt, is the result of the widespread distribution of pathological lesions throughout all of the viscera. To show the extent of this malnutrition we compared the weights of 77 syphilitic infants at the time of the first examination with the average weights of a like number of normal infants of the same ages: 7 were overweight, 10 of average weight, and 60 below average weight. The entire group of 77 cases averaged 1480 gms., or a little more than 3 pounds below weight. This wasting, or malnutrition, is of extreme importance, as the outcome of any individual case depends more upon the state of the infant's nutrition than upon the specific treatment.

Associated with this wasting the large part of the cases of infantile syphilis show one or more of three symptoms: a rash, a rhinitis or coryza, and a palpable spleen. The first was present in 77 per cent., the second in 74 per cent., and the third in 82 per cent. of the 100 cases in our series. These might be called classical symptoms and require no discussion, but in passing I might add that in our series a desquamative dermatitis, particularly of the palms of the hands and the soles of the feet, was far more common than a macular or maculopapular eruption. This is contrary to the teaching in most text-books.

Epiphysitis is a common lesion and can be demonstrated in many of the stillborn infants by incision through the lower end of the femur, or by a line of enlarged calcification seen in roentgenographs of long bones in infants with syphilis. In these cases nothing is visible clinically until the process extends to the tissues surrounding the bone and the muscles become involved. This produces "Parrot's pseudoparalysis," which is erroneously termed epiphysitis. This external involvement was present in 14 of the 100 cases in our series. A condition frequently overlooked is an iritis or choroiditis in early infancy. Everyone is familiar with the keratitis of "late" syphilis, but eye examinations, and particularly ophthalmoscopic examinations, of young infants are so infrequent that these ocular manifestations which we find quite frequently are missed in many cases.

Perhaps the question of greatest interest in connection with these syphilitic infants is their outcome or future; 40 per cent. of the infants in our series died in the first year of life, and this despite the fact that most of them received intensive treatment. Other observers report a similar or higher mortality, and I have not run across any lower figures. Among those who do not die a small number develop lesions which lead to permanent symptoms—cerebrospinal syphilis, etc.—and in the sense that these permanent changes are the result of syphilis may be said never to clear up. In about half of the cases the signs of the infection disappear, either as the result of treatment or seemingly from some inherent reason. Unfortunately these cases are, as a rule, lost from view.

In a certain percentage of children developing late lesions there is a history of infantile lesions, but it would seem that in some of these early cases the infection becomes latent or dies out. There are no statistics on record of how many infantile cases develop late lesions. Between the second and the fifth years relatively few patients with active signs of inherited syphilitic infection are seen, but from then on until puberty many cases are encountered. As stated before, but few of the late cases give a history of previous lesions and the infection seems to have been latent since birth in the majority. The factors which lead to the development of these acute cases in late childhood are unknown. We know that, as a general rule, any infection in childhood lowers a previously acquired immunity or resistance to some other infection, as the lowering of resistance to tuberculosis following measles, and it is probably in something of this nature that the explanation for the development of acute lesions in long-standing quiescent syphilis will be found. Trauma would seem to be a factor in some cases.

It is the growth in the past few years of the number of pathological conditions which have been shown to be the result of "tardy" syphilis that has made the study of inherited syphilis of so much importance and interest. In order to show the protean character the infection assumes in childhood, and how little related are the clinical conditions due to the same infection, I have tabulated the lesions occurring in 100 cases of late syphilis. These are made up of two series of consecutive cases, one of 74 reported one and a half years ago[8] and the last 26 cases admitted to the Children's Hospital.

BONES:		CENTRAL NERVOUS SYSTEM:[9]	
Periostitis tibia	4	Mental deficiency	23
Periostitis skull	1	Cerebrospinal syphilis	14
Osteomyelitis	1	Hemiplegia	6
JOINTS:		Epilepsy	5
Acute arthritis knee	8	Spastic paraplegia	4
Acute arthritis ankle	1	Chorea	2
SKIN:		Hydrocephalus	2
Macular eruption	1	MISCELLANEOUS CONDITIONS:	
Condyloma anus	3	Ozena	1
Gummata	3	Enlarged spleen (only symptom)	1
Alopecia	3	Torticollis	1
EYE:		Aortitis	1
Interstitial keratitis	24	Obscure abdominal pain	1
Choroiditis	1	Obscure pain in legs	2
ULCERATIONS:		Endarteritis obliterans	1
Nasal	2	Paroxysmal hemoglobinuria	1
Laryngeal	1	Raynaud's disease	1
Pharyngeal	1	Hutchinson's teeth	4

The thing standing out most prominently in this table is the great preponderance of syphilis of the central nervous system.

[8] Veeder and Jeans, Late Hereditary Syphilis, Am. Jour. Dis. Child., 1914, viii, 283.

[9] 47 patients showed lesions of the nervous system.

This is contrary to the usual teaching of hereditary syphilis. Holt, for example, in the last edition (1911) of his text-book says of hereditary syphilis, "The different lesions of the central nervous system which may be due to syphilis are all quite rare." In 47, or approximately one-half of our series of 100 "late" cases, the infection appeared in some form of lesion of this system. The other conditions, as periostitis, Hutchinson's teeth, arthritis, interstitial keratitis, etc., which are usually described as the most common, were all present in the series, but in a much smaller percentage.

I have gone over our records to find in what percentage some of these conditions have a syphilitic basis. Hydrocephalus has always been charged against a specific infection to a greater or less degree. Of 13 cases upon which we made Wassermann tests, 3, or about 23 per cent., were positive; 31 cases of epilepsy have been tested, and 6, or 20 per cent., gave positive reactions. Spastic paraplegia is most interesting, as only recently has there been a connection with syphilis suggested. Syphilis was present in 3 of 10 cases, or 30 per cent. in our records. Holt did not happen to meet with a single positive case in eight tested, but Findlay obtained 13 positive tests in a series of 33 cases examined. Hemiplegic children gave the highest percentage of positive reactions, 6 out of 12 cases, or 50 per cent., having syphilis.

A few years ago a French writer, whose name I have forgotten, reported that he had obtained positive reactions in nearly all of a small series of children with chorea. This was not confirmed by subsequent investigations, and it is probable that considerable error in the technic of making tests must have crept in. We have tested nearly 40 cases of chorea and in 2 obtained positive reactions. In 1 of these the chorea apparently had a syphilitic basis, but in the other it might have been a chance association. Neither had any signs of a rheumatic infection. The one case—a maniacal chorea—responded immediately to specific treatment. In order to see if the therapeutic test was of any value we treated several non-specific choreics in the same way without the slightest effect being produced. Comby[10] has recently reported that he found evidence of syphilis in 7 of 39 cases of chorea, but Koplik[11] in a smaller series came to the conclusion that there was no relationship between the two.

Mental deficiency has been a favorite subject of study from the standpoint of syphilis in the last few years, and with the most contradictory results when large groups of institutional defectives have been examined. What, from our view-point, is of more importance than the percentage of mental deficiency due to syphilis is the number of syphilitic children showing mental deficiency.

[10] Etiology of Chorea, Arch. d. Med. d. Enf., 1915, xviii, 517.
[11] Relationship of Syphilis to Chorea of Sydenham, Arch. Pediat., 1915, xxxii, 561.

Thus 23 out of 100, or approximately one-fourth of the "late" group, were defectives. In addition then to the high death rate of inherited syphilis we must add one-quarter of the living children as "worse than dead."

Recently a new test for the presence of protein substances in the spinal fluid has been advanced which it is claimed is of value in the differential diagnosis of cerebrospinal syphilis from other diseases of the *central nervous* system. This is the "colloidal gold" or Lange test, in which various dilutions of the spinal fluid under investigation are added to the reagent in a series of tubes. According to the discoverer of the test each disease produces a color change in certain tubes—or a zone of color change—which is characteristic of the disease. Thus in syphilis the zone of change is in the lower dilutions and in tuberculous meningitis in the higher. As yet the test has been almost exclusively used in the diagnosis of paresis and other parasyphilitic conditions. Dr. Meredith Johnston has been making a general study of the spinal fluid in childhood in our laboratory, and among his cases were 20 of hereditary syphilis. All of these gave a positive Wassermann on the blood. In 15 of the 20 cases the central nervous system was involved. In 14 of these 15 the Lange test was positive while the Wassermann was only positive on the spinal fluids of 8 of 14 tested. Thus only 1 case gave a negative Lange while in 6 the Wassermann was negative. Both the Wassermann and Lange tests were negative on the spinal fluids of all 5 cases without clinical signs of central nervous involvement. The only other disease which Dr. Johnston has found which gives a similar zone of change to that occurring in cerebrospinal syphilis is acute anterior poliomyelitis, and in this the reaction is only transitory and not persistent as it is in syphilis.

Wassermann Reactions. From what has been said it is obvious that we attach a great deal of importance to the Wassermann reaction. Like all delicate laboratory tests it is only of value when carefully controlled and made by a skilled technician. A poor Wassermann test, or one in which there is a question as to the accuracy of the worker, is worse than none, while a good test is of great value. We look upon a Wassermann reaction as a symptom or an indication of infection rather than of immunity, and in this sense it is comparable with the tuberculin reaction. When a case of syphilis is cured the reaction becomes negative, but the patient again becomes susceptible to infection, and a number of cases have been reported where this has taken place. The longer the infection has been present the more apt is the reaction to be positive, hence the high percentage of positive reactions in tertiary and parasyphilis, and likewise in inherited syphilis. We have seen but one patient with late hereditary syphilis whose blood failed to give a positive reaction, and in this the diagnosis was somewhat ques-

tionable. For practical purposes then we can say that in our experience all of the cases of late hereditary syphilis give a positive reaction. This does not hold true for the cases of an infantile type. In the series of 100 cases reported above the blood was tested in 82 with the following result:

Positive	76 or 92.6 per cent.
Doubtful	1 or 1.3 " "
Negative	5 or 6.1 " "

For the two types (over 300 cases) the percentage of positive reactions is about 98. This corresponds with the figures of Boas,[12] who states in his book on the Wassermann reaction that hereditary syphilis gives a higher percentage of positive reactions than the other forms. He tested 53 infants with manifest lues and 54 older children with late lesions and all reacted positively. A number of newborn syphilitic infants reacted negatively, although most of this type of cases gave a positive reaction. A number of writers have called attention to the fact that a small percentage of newborn infants give a negative reaction and later a positive one. This may be explained on the basis that infection occurred just before birth and that some time must elapse before the formation of reactive bodies. Three of the five negatively reacting infantile cases in our series do not belong in this group, as two were three months of age and one five months when tested. All were clinically syphilitic and there was syphilis in the parents of the one child whose parents submitted to tests. Positive reactions in non-syphilitic children are rare, so rare I feel the technic must be faulty. I can recall having seen but one such case, and this reacted negatively on a control test. Lederman found 3 in 650 non-syphilitic infants, and these might have been latent cases. Occasionally a weakly positive transitory reaction has been reported in scarlet fever, pneumonia, influenza, and other infections. We have tested a number of scarlet fever cases as well as other febrile conditions without finding a single positive reaction.

We can say then that positive reactions in non-syphilitic patients are extremely rare, that in all of the patients with the late type and over 90 per cent. with the infantile type of hereditary syphilis the Wassermann reaction is positive. It is understood, of course, that these figures refer to untreated cases.

My personal experience with the luetin test of Noguchi is very limited. It most certainly cannot offer any advantages over the Wassermann reaction insofar as the furnishing of diagnostic information in hereditary syphilis is concerned, and as we have had dependable laboratory workers making tests we have neglected the luetin test. Its simplicity offers great practical advantages.

[12] Die Wassermannsche Reaktion (2d ed., Berlin), 1914, p. 119.

Recent reports have been somewhat more favorable than the early ones, but the opinion is quite general that the Wassermann reaction is the preferable of the two.

TREATMENT. In general we are accustomed to regard hereditary syphilis as a disease particularly amenable to treatment. If we judge the results of the treatment by its immediate effect upon clinical symptoms this holds true, but it is not true when we consider treatment in its relation to the ultimate cure of the disease. Most acute hereditary syphilitic lesions disappear rapidly under specific treatment with the exception of interstitial keratitis, but the chronic lesions of the central nervous system are but little affected. It is extremely difficult to obtain a persistently negative Wassermann reaction as the result of treatment, and particularly so in the "late" cases. We have treated some cases intensively and persistently for over three years without effect. We have obtained negative Wassermann reactions in the infantile cases following intensive treatment, but in surprisingly few cases considering the entire number treated. In these "infantile" cases, as a matter of fact, the outcome of the case, as far as life or death is concerned, depends far more on the condition of the patient's nutrition than upon the character of the specific medication. If a long series of cases are studied it will be found that the therarpeutic results are disappointing as a whole.

We have used various methods of treatment in our cases, including over 100 in which neosalvarsan was used in combination with mercury. It is the drug of choice to make an acute lesion—as a rash or an arthritis for example—disappear in the shortest time, but for the long-continued treatment which is necessary mercury is preferable. The most satisfactory form of mercury for use with children in our experience is gray powder.

REPORT OF A CASE ILLUSTRATING THE ANATOMICAL SEAT OF MOBILE SPASMS.

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AND

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THE following is the history of the case of a child who, from the age of six months to the sixth year when he died, suffered from continual choreic and tonic spasms, involving nearly all the muscles of his body, including the neck and face.

The case has this importance that it shows an anatomical seat of such spasms as those of chronic chorea, of spasmodic tics, and of myotonia.

SUMMARY. A child, aged six years, born prematurely; normal until the fourth month; then an attack of stupor, etc., diagnosed as "meningitis," then development of clonic and tonic movements involving face, throat, neck, trunk, arms, and legs, the legs being mainly rigid, so that the child could only imperfectly stand or walk; no paralyses, no atrophies, no anesthesias, special senses normal, intelligence retarded, but not seriously.

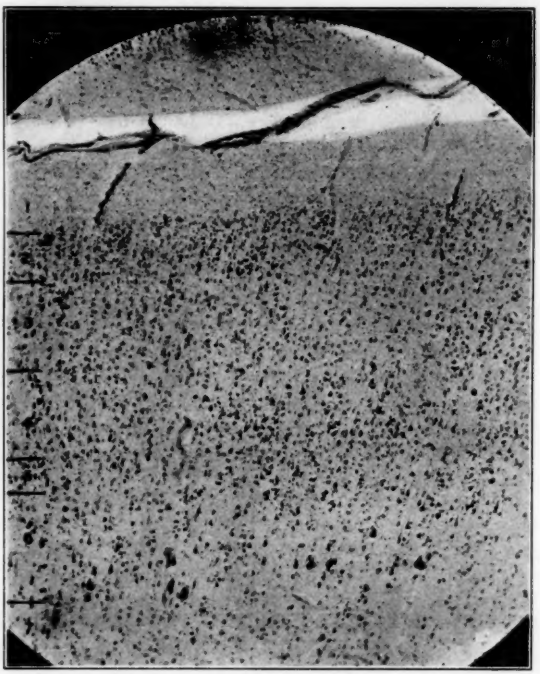


FIG. 1.—Anterior cerebral convolution; arm area × ⅔. Compare Fig. 14. The lines on the side indicate approximately the cortical lamina of this area according to Campbell.

Duration of condition five and one-half years. Death following operation to resect posterior spinal roots.

Autopsy. No gross lesion of brain or cord; brain of normal size and weight.

Microscopically the motor and premotor cortex showed disturbance in lamination of cells, degenerative changes of cells, deficiency

in size and number of large pyramidal cells. Changes less marked in posterior central convolution. Changes similar to those of ante-

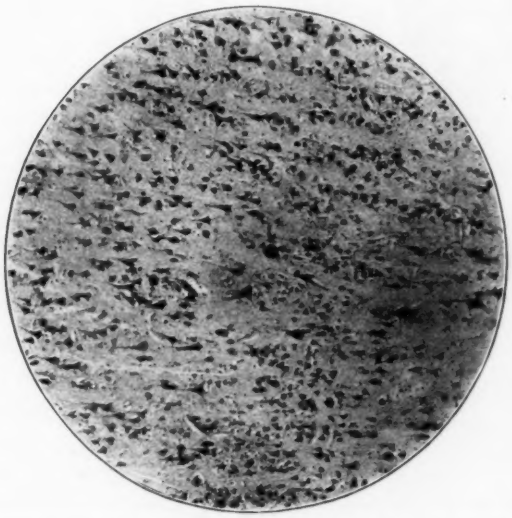


FIG. 2.—Anterior central convolution; arm area × $\frac{1}{130}$, showing fourth, fifth, and sixth layers.

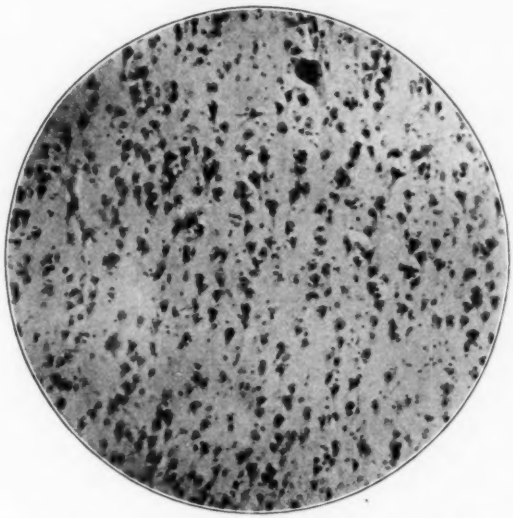


FIG. 3.—Anterior central convolution; arm area × 200.

rior central convolution though much less marked in the thalamic and subthalamic region. Nuclei of columns of Goll and one pyramidal tract show some deficiencies.

The tonic and clonic spasms with some permanent rigidity of the lower extremities were the main features of the case. The tonic spasms caused an apparent spastic paraplegia, although there was no real paralysis, nor objective evidence of involvement of the pyramidal tracts, and both the corticospinal and the peripheral motor neurons showed no or slight signs of degeneration.

History. K. R., male, aged three years and eleven months was brought to me for consultation by Dr. Morissy, of Connecticut. He is the second of three children. The parents are healthy with no history of lues. The boy was born prematurely (six weeks before the time) with a rather long labor, but without any instruments. He had no convulsions, and he grew like a normal child until he was about four months old, when he was taken with what was called "meningitis" and was ill in bed for several weeks. He had a number of convulsions at that time and was in a stuporous condition

After coming out of this he began to develop clonic and tonic spasmodic movements involving the face, tongue, neck, trunk, and extremities; these continued without interruption.

He was first seen by me in April, 1909, when he was three years and eleven months old. He was then fairly well grown but poorly nourished.

His body and extremities, neck and face were in continuous spasmodic movements. The legs were kept mostly in extension, but there was no permanent and absolute contracture and he could at times support himself and with much help could walk a little.

He could not hold up his head, sit up or stand alone, mainly because of the continuous spasms. The head and neck were particularly affected with clonic and tonic spasms of the right accessory which pulled it toward the left as in wry-neck. There were also retrocollic spasms which pulled his head backward; also spasms of the facial muscles and of the tongue, so that he spoke only indistinctly, though he could talk a little. He understood what was said to him, and though somewhat retarded, he seemed to be fairly intelligent. The eye muscles were not involved, the special senses of vision and hearing were normal.

The limbs were well developed and rather muscular, but were in a spastic condition much of the time. The arm movements were jerky and irregular, and he could not easily bring his hand to his mouth or perform any purposeful acts.

The deep reflexes were exaggerated, and there was a doubtful dorsal toe reflex, but no ankle clonus. There was no anesthesia, superficial or deep.

The boy had a normal sized head, but there was a slight bilateral

depression in the skull over the motor area on each side. He had a narrow palate and shell ears.

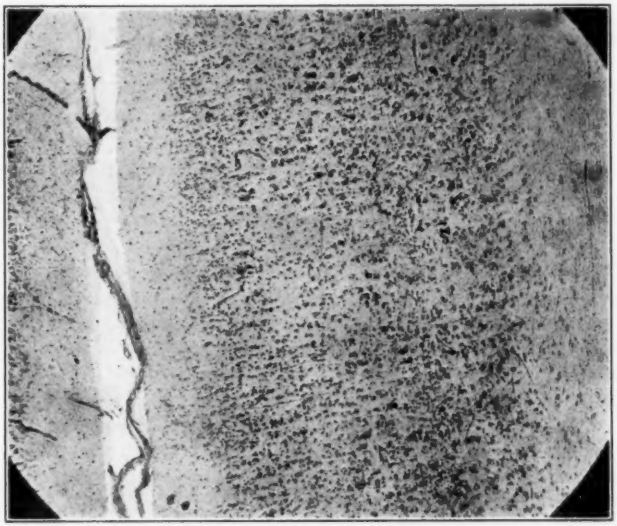


FIG. 4.—Posterior central convolution; arm area × ⅔.

FIG. 5.—Posterior central convolution: arm area × 130.

Three years later the child was brought to me again and sent to the Neurological Institute (December 12, 1912). At that time the following notes were made upon him:

"Child pitifully undeveloped and under nourished. Is seen lying always with the head turned to the right, his arms flexed upon the elbows, his hands clenched, and these tossing and beating about his face and head. The arms can be straightened only with force and then resume their contractured position at once, unresisted.

"The trunk is more quiet than the head or arms and the legs do not move about like the arms, but are held extended partly with the knees slightly flexed. When the child is lifted and his feet brought to the floor he makes no attempt to support himself, and his head is drawn far backward upon the shoulders.

"At the sight of food when hungry the child's movements become greatly increased, the mouth opens widely on the left, the right side hardly sharing in the movement; the hands beat widely about the mouth as though some attempt were being made to assist himself. The feeding of the child is therefore difficult. It is best accomplished by two persons, one to hold him in the sitting position with the back and head supported and his arms clasped in a towel or blanket to prevent them from jerking into his face and mouth spasmodically, and the other person to bring the milk to his mouth in small quantities.

"He cries repeatedly for his mother (a sound similar to 'udda'), and when asked if it is his mother he means, he quickly answers 'ya.' When given a toy rooster in a cage and told what it is, and then later asked to name it, he calls out at once 'oota;' and when he hears an imitation of the crow of a rooster a fleeting smile occurs on the right side of the face alone while during the whole event the arms are moved violently about the ears and face.

"He understood what was said to him and tried to make his wants known."

In addition to the foregoing the following notes were made upon his cranial nerves:

III, IV, VI not involved.

Motor V and sensory V not involved.

Motor VII tonic spasms produced compression of the lips with irregular clonic movements.

VIII normal.

IX, X, XII slightly irregular movements of the tongue, throat, and palate.

XI very violent tonic and clonic spasms of the spinal accessory, the left more than the right.

I to IV spinal nerves: rotators slightly involved.

V to VIII spinal nerves: tonic spasm, adducting arms, flexing forearms, supinating forearms, extending wrists, flexing fingers: The flexing spasms alternate with some extensor spasm and there

are also twitching, oscillating and rhythmic movements, causing the head to be twisted and retracted.

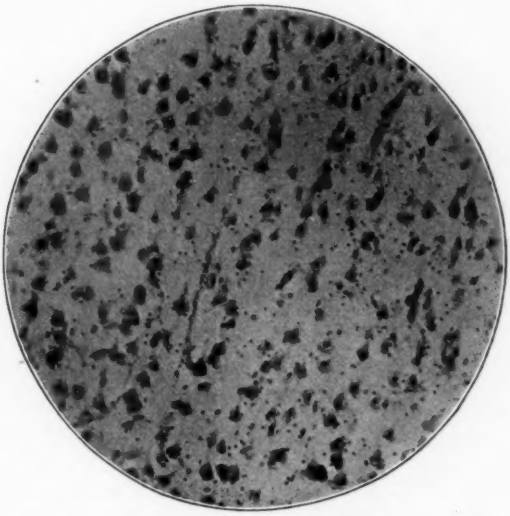


FIG. 6.—Posterior central convolution; arm area × 200.

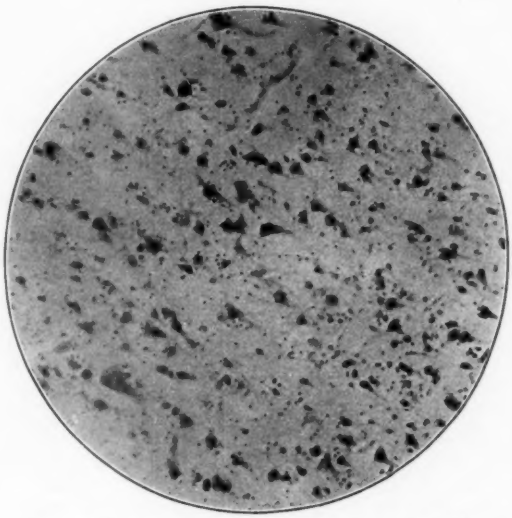


FIG. 7.—Anterior central convolution; leg area × 200.

The most violent movements seemed to be thus involving the neck and arms, and therefore it was thought possible to produce some relief by resecting the posterior roots of this region.

The operation was undertaken with great care by Dr. A. S. Taylor, but the child suddenly stopped breathing and died on the table.

Operation (reported by Dr. A. S. Taylor).

A left unilateral laminectomy was done, involving the 5th, 6th and 7th cervical vertebræ. There was no special difficulty in doing the laminectomy, but there was far more profuse hemorrhage than usual.

The dura was exposed when he suddenly stopped breathing. The heart continued to beat for some time. Artificial breathing was kept up for some time, and saline infusion was given when the heart gave signs of failing, but all to no purpose.

As to the cause of death, the hemorrhage was undoubtedly one factor. The operation had taken only twenty minutes up to that time, so it would not seem fair to hold the anesthetic nor the time consumed in any way responsible.

The unknown factor in the result might be termed lymphatic diathesis, or some of the other names with which ignorance is properly clothed.

Pathological Findings (by Dr. Gere). Examination of the specimen, upon which the clinical and pathological studies of this case rest, showed to the naked eye a brain of apparently normal development in a child of six years, symmetrical in its lateral halves, the convolutions, generally, were deep and full and exhibited no evidences of localized atrophy.

Measurements of the cerebrum, taken after fixation in formalin, may be given as 15 cm. in its anteroposterior diameter, while the greatest transverse diameter measured 11 cm. The weight cannot be accurately given, but, after immersion, one cerebral hemiphere weighed one-half kilo.

The membranes appeared normal except for a mild basilar meningitis, more apparent microscopically than to the naked eye.

The areas inspected include the motor cortex, the postcentral convolution, the thalamic and subthalamic regions, the basal ganglia, red nucleus besides sections through each of the nuclei of the cranial nerves; the spinal cord was also sectioned at different levels.

In observation of the motor cortex attention is directed in a general way to a rather indiscriminate arrangement of cells below the layer of medium-sized pyramidal cells to an apparent diminution in the number of cells of large size, to the difficulty in defining, strictly, cell lamination, and to the distortion of individual cells with, in many instances, an absence of dendritic processes.

Interspersed are to be found many cells preserving their normal pyramidal form and others in varying stages of degeneration.

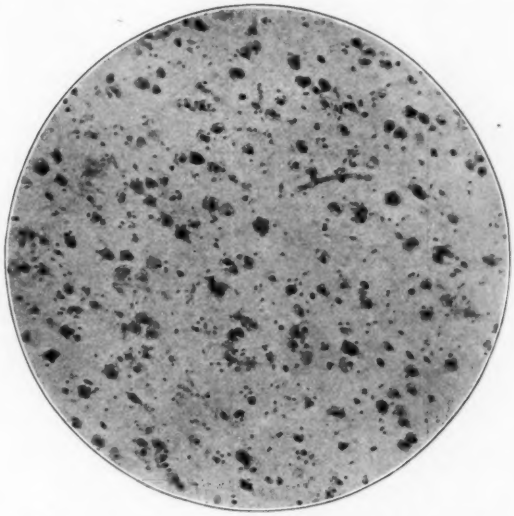


FIG. 8.—Posterior central convolution; leg area × 200.

FIG. 9.—Medulla; region of twelfth nerve.

The degenerative process is shown by a tigrolysis varying up to a complete destruction of the chromophylic granules; the nucleus in many of the partly degenerated cells is preserved and placed eccentrically, while the remaining granules are piled up at one pole. A deficiency in size, number, and arrangment of the cells of Betz is very striking.

Inspecting the lamina in order, the plexiform layer does not appear to be disturbed and the cells of the second and third layers are normal except for a few more or less degenerated cells in which the processes are not strongly marked. The layers of large pyramidal cells are not always well defined but appear confused. In the deeper layers of the cortex are many degenerated cells.

In the postcentral convolution cell lamination is far more distinct and the disturbance is present in a slighter degree, though here too, are many degenerated cells lying deep in the cortex.

The thalamic and subthalamic regions and the basil ganglia show nothing remarkable in cell formation and arrangment, and there is no degeneration of cells of the nuclei of the cranial nerves, but the eccentric position of the cell nucleus with the peculiar clumping of the chromophylic granules is, in many cases, pronounced.

Though the clinical history makes note of difficulty in swallowing and of convulsive movements of the face, both the hypoglossal and facial nuclei of each side present no abnormality.

Other nuclei in the region of the hypoglossal, namely, the ninth and tenth, in both the motor and sensory divisions appear entirely normal; nor are changes demonstrable in the sixth, fifth, fourth or third nuclei.

The cells of the anterior horns of the spinal cord from the first cervical segment to the sacral region are normal, but the posterior column nuclei show a few worn cells similar in appearance to those observed in the postcentral and motor areas.

The corticospinal pyramidal system shows no degeneration, but there is a deficiency of medullated fibers in one lateral pyramidal tract throughout the cord. Similarly there is a deficiency without degeneration of the posterior columns, particularly in the columns of Goll in the upper lumbar, the dorsal and cervical regions. In the medulla the arcuate fibers and median lemniscus are well developed and present no pathological changes.

The third and lateral ventricles of the brain are not dilated, and exhibit a thickened subependymal tissue with a tendency to gliosis, though the ependyma itself appears normal, and this is also true of the Sylvian aqueduct, which is very irregular in outline and sacculated.

In the region of the posterior corpora quadrigemina and placed ventral to the aqueduct of Sylvius there appears a formation resembling an obliterated canal by ependyma.

Changes similar and more intense are to be observed in the fourth ventricle, especially in its posterior extremity, where a condition of gliosis undoubtedly exists.

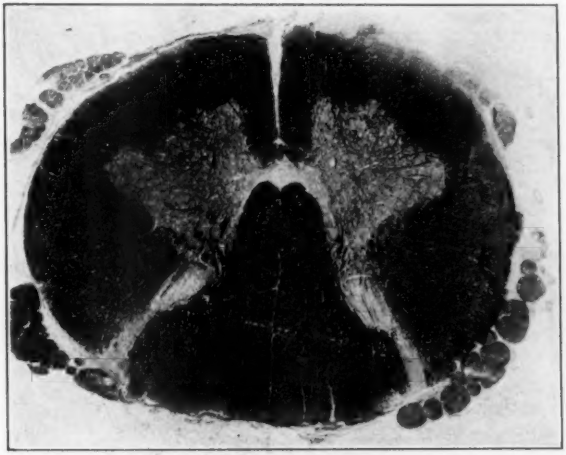


FIG. 10.—Spinal cord, cervical region.

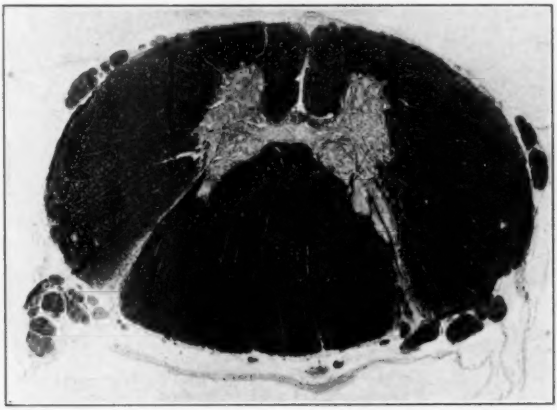


FIG. 11.—Upper dorsal cord.

The choroid plexuses present no particular pathological change.

The cerebral vessels are the seat of marked changes which consist of thickened walls, distended perivascular lymph spaces containing many deposits of round cells.

Examination of the cerebellum fails to demonstrate any departure from the normal structure of that organ.

The observations in the above report were confirmed by Dr. James Ewing and Dr. T. H. Ames.

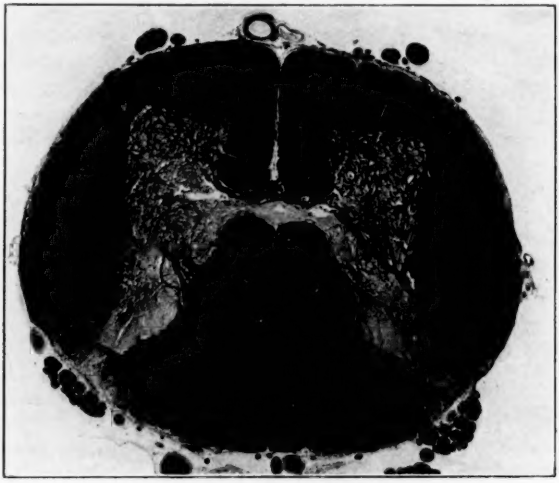


FIG. 12.—Lumbar cord.

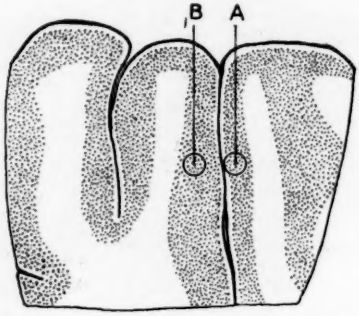
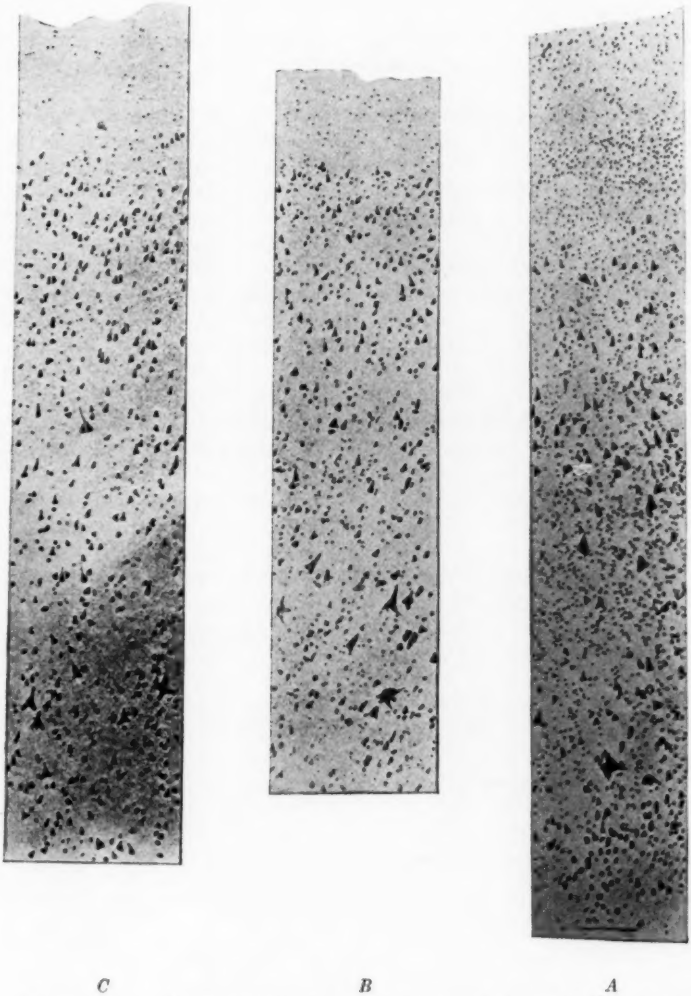


FIG. 13.—Anterior (*B*) and posterior (*A*) central convolutions—arm area—showing location of areas photographed.

The conclusions from this case are that the patient had at the fourth month a low grade infectious polioencephalitis affecting especially the motor cortex and impairing the sensori-motor mechanism, *i. e.*, the dendrites and fibrils. This led not to paralysis but to irregular motor discharges and loss of muscular control.

The existence of an abnormally fine pyramidal tract is probably

due to some slight involvement of the cells of Betz, and this might perhaps explain spasticity and weakness, but not the various types of mobile spasm seen in the case reported here.



C *B* *A*

FIG. 14.—*A*, section through the anterior central convolution of a healthy brain; *B* and *C*, sections through the anterior central convolutions of two cases of cerebral spastic hemiplegia with intact pyramidal tracts. One sees in both cases that the deep layers are hardly affected, while the superficial layers are markedly atrophied. (H. Vogt.)

The subject of cerebral hemiplegia and diplegia without involvement of the pyramidal tracts is discussed in full with bibliography by Dr. H. Vogt.[1] In these cases, sometimes at least, the spastic paralysis seems due to atrophy of the superficial layers of the cortex with intact cells of Betz (Fig. 13). In our case it was not so much atrophy of particular layers, but various irregular displacements, degenerations, and focal atrophies. This would explain the irregular motor discharges.

The cortical changes that were found are sufficient to explain the spasmodic symptoms, and as these lesions were induced by some infection four months after birth it is a fair inference that they were primary and not secondary factors in the disease. We believe that they give us an indication of the pathological anatomy of the chronic degenerative myoclonic and myotonic spasms.

It seems to be fairly well established that the chronic, coarse, jerky, ataxic tremors are due to involvement of the cerebellar rubrospinal and extrapyramidal tracts. Such involvement is seen in paralysis agitans, multiple sclerosis, and midbrain and cerebellar disease.

But the clonic and tonic spasms such as are seen in spasmodic tics, torticollis, hereditary chorea, and myoclonias especially are cortical and due to defects and displacements of the cells of the central and precentral convolutions.

This view is supported by the fact that cortical changes are found in chronic and hereditary chorea, in myoclonus epilepsy and in certain localized degenerative tics.

The case presented clinically some of the features of Little's disease, with clonic and tonic spasms, but there was in our case no real paralysis and no involvement of the pyramidal or extrapyramidal tracts, at all adequate to explain the essential features of the symptoms.

A study of the types of cerebral infantile diplegia without anatomical findings has been first and elaborately made by Dr. William G. Spiller.[2]

A full bibliography of this subject is given as stated above by Dr. H. Vogt.

[1] Lewandow's Handbruch de Neurologie, vol. iii, p. 295.

[2] Jour. Nerv. and Ment. Dis., 1898, p. 81; Univ. Penna. Med. Bull., January, 1905, by Dr. John H. W. Rheim; AMER. JOUR. MED. SC., December, 1909, and later by Berghinz, Revista di Clinica pediatrica, 1903, p. 416.

THE RELATION OF THE HYPOPHYSIS TO CERTAIN CLINICAL MANIFESTATIONS AND THE THERAPEUTIC APPLICATION OF ITS EXTRACTS.[1]

By Joseph L. Miller, M.D.,
CHICAGO.

During the past ten years there has developed a very extensive literature dealing with the role of the hypophysis in the animal economy. No attempt will be made to even review this investigation, but rather to consider only certain clinical manifestations which may be associated with disturbances in the hypophysis and the therapeutic application of its extracts. In this group may be considered acromegaly, dystrophia adiposogenitalis, or Fröhlich's syndrome, possibly adiposis dolorosa, or Dercum's disease, diabetes insipidus, and glycosuria.

It has been very clearly shown that the hypophysis is essential to life. Animals survive its complete removal only a few days, or at most a few weeks (Paulesco, Cushing, Biedl). When the posterior lobe alone is removed, permanent recovery without symptoms or disturbance of development occurs. As shown by Cushing and his colleagues, when only a portion of the anterior lobe is removed the animal may recover, but gradually develops a group of disturbances resembling very closely Fröhlich's syndrome as observed in man. The animal becomes very fat, the hair is thinned, atrophy of the testes or ovaries occurs, and the sexual activity is lessened or disappears. In the case of puppies there is failure of skeletal development and adiposity and sexual infantilism. It is apparent from these observations that it is the anterior lobe of the hypophysis that is essential to the life of the animal, its complete removal resulting in death, its partial removal in developmental disturbances. On the other hand it is only the extracts of the posterior lobe that have been demonstrated to be therapeutically active. Strictly speaking, this active substance is only present in the pars intermedia of the posterior lobe. This extract when administered intravenously or intramuscularly to man affects the cardiovascular system, the kidney, uterus, urinary bladder, intestine, and the secretion of the mammary gland.

Acromegaly. Marie, in 1886, first called attention to the probable relation between acromegaly and the hypophysis. Previous to this time mention had been made of the increased size of the hypophysis in pathological giants. Changes in this organ have no doubt been responsible for many of the giants in history, as a study of the sculpture on certain French and Italian churches

[1] Read before the Chicago Institute of Medicine, January, 1916.

shows that the giants figured there are in reality acromegalic individuals. When certain disturbances of the hypophysis occur early in life, gigantism follows, these same changes arising after maturity gives rise to acromegaly. It is stated that after castration there is a hyperplasia of the hypophysis, and it is well known that many eunuchs attain unusual height.

Without entering into a detailed discussion of this subject it may be said that at the present the generally accepted view is that acromegaly, like gigantism, is due to overfunctioning of the anterior lobe of the hypophysis. This may be accompanied by an actual enlargement of this lobe or simply by an increase in the specific glandular secretory cells. There is some evidence to show that certain types of dwarfism may be due to hypofunctioning of the anterior lobe. Quite numerous feeding experiments on young animals with anterior lobe substance have failed to show any general modification of growth, but increased rapidity of growth of the sexual organs (Goetsch). Feeding the posterior lobe has no effect on growth.

Dystrophia Adiposogenitalis, or Fröhlich's Syndrome. This condition, first described by Fröhlich in 1901, had as its chief clinical manifestations, adiposity, scant growth of hair, dryness and lowered temperature of the skin, trophic disturbance of the nails. When it occurs before maturity, failure of development of the bony skeleton, infantilism or sexual atrophy, in woman lessened or absent menstruation, and in man impaired sexual desire. While acromegaly and Fröhlich's syndrome thus differ materially in their clinical manifestation the two groups of disturbances may be present in the same individual. Many acromegalic individuals are adipose, have less sexual power, etc. According to Creutzfeld, sexual atrophy is observed in 36 per cent. of acromegalics and adiposity of the Fröhlich type in 1.5 per cent. of cases. The association of these three disturbances of development might lead one to infer that they had a common origin, *i. e.*, were due to disturbance in the same portion of the hypophysis. Inasmuch as one of these, acromegaly, is quite certainly due to disturbance of the anterior lobe, is it not probable that all of these developmental abnormalities have the same origin? Fröhlich, Fischer, Cushing, Falta and, in fact, practically all writers on this subject, have ascribed Fröhlich's syndrome to disturbances in the posterior lobe, this being in the nature of a hyposecretion. Cushing and his colleagues maintain that lessened functioning of the posterior lobe gives rise to increased sugar tolerance, and that this is a possible factor in the adiposity. It is difficult to see how, with the evidence at hand, such deductions are justified. The anatomical findings in the majority of these cases is of a new growth, either in the hypophysis or its immediate neighborhood—a type of tumor, however, different from that present in acromegaly, where adenomatous growths predominate,

but rather destructive processes, as sarcoma, carcinoma, glioma, cysts, etc. In the 34 cases autopsied and reported by Biedl, 23 showed a tumor of the hypophysis and seven times a tumor in the region of the hypophysis. In at least one case the hypophysis was macroscopically normal. A study of the hypophysis in these cases has thrown very little light on the subject on account of the involvement of both lobes, either directly by the growth or indirectly by pressure or circulatory disturbance. The rare but still occasional association of adiposity with acromegaly might be interpreted as speaking against a common origin, viz., the anterior lobe for these two disturbances. These two conditions, however, are both developmental in character, one selecting the bony skeleton, the other the soft parts. It would not be more unusual, as Strada has stated, than the occasional association of myxedema and hyperthyroidism in the same individual. It is not necessary, however, to conclude that lessened secretion of the anterior lobe is responsible for the Fröhlich syndrome. There may occur a modification of the secretions due to a change in the character of the cells in the anterior lobe, as has been noted during pregnancy, where there occurs a great increase in the chromophobe cells with marked change in their histological character and quite probably change in the character of their secretion. At the same time there is a corresponding reduction of the chromophil cells. Accompanying these changes there is often a tendency to adiposity and especially rather marked and characteristic thickness of the face. The most convincing evidence, however, that Fröhlich's syndrome is due to the anterior lobe is furnished by the experimental findings in dogs. Removal of the posterior lobe is not followed by any serious consequences, the animals recover and later fail to show any anomalies of growth (Paulesco, Cushing, Ascola). However, when a considerable portion of the anterior lobe of a young dog is removed, and the animal recovers from the operation, he later develops the Fröhlich syndrome of delayed development, adiposity, and failure of sexual development. This evidence is very conclusive and to my mind far outweighs all our other information. While it is too early to say that Fröhlich's syndrome if associated with the hypophysis must be due to disturbances of the anterior lobe, it seems highly probable that eventually this will prove to be the case. The anterior lobe would then be responsible for all developmental anomalies; the function of the posterior lobe to furnish secretions which affect the cardiovascular apparatus, the kidney, the uterine, intestinal, and urinary bladder contractions and the secretion from the mammary gland.

Organotherapy in the treatment of Fröhlich's syndrome has not given very definite results. Cushing has reported a few cases where the administration of the entire hypophysis has caused reduction in weight and an improvement in the mental condition. Reported

changes in the mental condition in this class of patients must be accepted with a certain amount of reserve, as the parents or friends of the mentally defective are usually most optimistic when an effort is made by the physician to improve conditions. Cushing, in his cases, has administered 9 grains daily in divided doses of the powdered entire gland. Patients with hypophyseal tumor and Fröhlich's syndrome, after operative removal, have been relieved of the pressure symptoms, but little change has occurred in the adiposity, growth of hair, or sexual condition.

Adiposis Dolorosa, or Dercum's Disease. Only passing mention will be made of the possible relation of this condition to the hypophysis. Falta has collected from the literature 11 cases with autopsy. Three of these had hypophyseal tumors and 4 others on microscopic examination pathological changes of a variable character. Hyperplasia of the cellular elements of the anterior lobe was found in some and in others increased connective-tissue formation. Even more constant pathological changes have been detected in the thyroid of these individuals, and it is too early to state whether either or both of these glands have anything to do with Dercum's disease.

Diabetes Insipidus. Magnus, Schaefer, and Herring first called attention to the diuretic action of extracts from the posterior lobe. This action, they reported, is partly due to dilatation of the renal vessels and in part due to direct stimulation of the renal cells, and apparently independent of any direct effect on blood-pressure. The diuresis continues long after the blood-pressure has returned to normal, and could still be excited after repeated injections, which result in a fall in pressure. In some instances diuresis occurred without increase in the size of the kidney, showing that it could not be due to renal dilatation but probably a result of increased activity of the renal cells, although, as a rule, dilatation of the renal vessels was associated with the increased urinary output. In these first experiments Schaefer and Herring worked with cats, using the extract intravenously and report quite constant evidence of diuresis. In dogs, however, in 7 out of 19 experiments, instead of diuresis, a diminished flow of urine was observed. With rabbits 2 out of 16 had a diminished urinary output after the intravenous injection of the extract. They explain this phenomenon by the presence of both a constrictor and dilator substance for the renal vessels; when the former predominates lessened urinary output results. When given subcutaneously to cats, diuresis was observed in only 25 per cent., of the tests, and when given by mouth, diuresis was never observed. To show the fallacy of therapeutic reasoning, after the publication of Schaefer's work, extracts of the hypophysis were placed on the market and recommended as diuretic when taken by mouth. At this time we made some clinical observations with this extract and found that even when given in very large

doses it had no diuretic action. Von Velden has shown that pituitrin, when given subcutaneously in doses of 0.5 c.c. to normal individuals, never excites diuresis, but, on the other hand, lessens the urinary output. This reduction at times may reach 50 per cent. During the past three years, at Cook County Hospital, we have studied the effect of pituitrin given subcutaneously in considerable number of cases of both normal and nephritic individuals, and in none of these have we been able to demonstrate a diuretic action. When any effect was observed on the urinary output it was invariably a reduction. From observations made in a patient with diabetes insipidus, using intravenous injection, it would appear that lessened urinary output results from this method of administration. Von Velden has also shown that following its use there is a marked reduction in the Nacl output but no constant effect on the phosphorus or nitrogen excretion.

This effect of posterior lobe extract is in perfect harmony with the findings in diabetes insipidus, and furnishes additional evidence that one of the activities of the hypophysis is to inhibit the activity of the kidney.

Diabetes insipidus may be produced experimentally by a variety of procedures. Bernard first demonstrated that puncture of the floor of the fourth ventricle just anterior to the glycosuria center would cause marked polyuria. Kahler reports there is no part of the cerebellum, pons, or medulla where experimental lesions may not excite marked polyuria. In addition cutting the greater splanchnic nerves in dogs gives rise to marked polyuria.

Clinically the most frequent cause of diabetes insipidus is lesions of the cerebrum, tumors at the base of the brain, and especially syphilitic basilar meningitis. That lesions of the hypophysis are a frequent cause of diabetes insipidus has long been suspected as diabetes insipidus is a frequent complication of acromegaly and dystrophia adiposogenitalis. It is very frequently associated with bitemporal hemianopia, a finding highly suggestive of a hypophyseal lesion. Kraus in 34 cases with bitemporal hemianopia found associated diabetes insipidus in 7 and Steinhaus in 50 cases, diabetes insipidus in 11. Simmonds, in Hamburg, has recently reported the interesting observation that in 500 autopsies he found 9 metastatic carcinomas, all in the posterior lobe of the hypophysis, and in 3 of these there was a history of diabetes insipidus. He refers especially to the frequency with which metastases are found in the hypophysis in mammary carcinoma. Erdheim has also reported diabetes insipidus due to a metastic growth in the hypophysis from a primary breast tumor. At present I have made under observation a patient who was operated on for carcinomaof the breast a year ago and who is now complaining of a marked polyuria, and my attention has recently been called to another case with diabetes insipidus associated with a mammary carcinoma.

These observations are of special interest by reason of the tumor being found in the posterior lobe. On account of the hypophysis being encased in the sella it is often difficult to determine when a tumor is present, whether the symptoms arise from the lobe involved, or as a result of pressure on the uninvolved portion. In several of Simmond's cases, however, the tumor was so small that it could have exerted little if any pressure. It is also only reasonable to assume that the effect on the lobe would be to lessen its functional activity. This point is of considerable importance as following the reports on the supposed diuretic action of the pars intermedia, Schaefer, Frank, Cushing and others have endeavored to explain hypophyseal diabetes insipidus on the overactivity of the posterior lobe. Animal experimental work does not furnish any very clear-cut evidence. After complete hyposectomy there is, as a rule, only a transient polyuria lasting two or three days. In a few of Cushing's dogs this was prolonged for a week. With complete removal of either the anterior or posterior lobe this same transient polyuria was observed, but never after any of the removals was there a permanent marked polyuria. These results are the same as those obtained by Schaefer after stimulation of the hypophysis with the thermocautery, as after this procedure a polyuria of three or four days' duration was observed. As far as can be determined from the literature no one after partial or complete removal of the hypophysis has produced a permanent polyuria resembling diabetes insipidus. Cushing's work shows, however, that when one of these polyuric dogs received hypodermically an extract of the posterior lobe that with few exceptions it was followed by a lessened output of urine. Thus furnishing evidence that in dogs, as in man, in conditions of polyuria extracts of the posterior lobe reduced the urinary output.

The most conclusive evidence that diabetes insipidus when associated with the hypophysis is due to lessened rather than increased secretion of the posterior lobe is furnished by clinical observation. Frank, Biack, Farini, Sereboullet, Hoppe-Seyler, von der Velden, Lichtwitz, Shomeyer, and others have shown that in diabetes insipidus the subcutaneous injection of extracts of the posterior lobe will lessen the urinary output 50 or more per cent. When 1 c.c. of pituitrin is given twice daily this lessened output may be maintained apparently indefinitely. With the diminished amount of urine there is an increased specific gravity, and, as C. Velder has shown, a lessening of the chloride elimination, but no material change in the total output of phosphorus or nitrogen. A patient recently under our observation had diabetes insipidus of eight years' duration, probably due to syphilis. The average urinary secretion was 5 liters. When given twice daily a subcutaneous injection of 1 c.c. of pituitrin there was a drop in urine to 3 liters with increase in specific gravity. The blood urea-nitrogen

before the use of pituitrin was high (31 mg. per 100 c.c.). After the pituitrin had been used several days the urea-nitrogen fell to 22 mg. As this was a single observation it is of little value, but of interest as showing in this particular case with the reduction of water output there had been an increased urea elimination. Following a single intravenous injection of 0.7 c.c. the urinary output during the following twenty-four hours fell to 1100 c.c., and the patient stated that for the first time in eight years he had not risen in the night to urinate. Large amounts of pituitrin by mouth and 0.3 gm. doses of powdered anterior lobe by mouth were without effect.

Glycosuria. It is generally conceded that patients with acromegaly very frequently show either a transitory or permanent glycosuria. Borchard collected 176 cases of acromegaly from the literature in 63 (or 35.5 per cent.), of which sugar was found in the urine. In 5 additional cases there was a definite alimentary glycosuria. Schlesinger and Borchard and Cushing have reported single cases in which, in the later course of the disease, the lessened sugar tolerance was changed to an increased tolerance. Inasmuch as acromegaly is thought to be associated with hyperplasia of the posterior lobe, it might be assumed that this portion of the gland was responsible for the glycosuria. Cushing, however, expresses the view that the glycosuria observed in acromegaly is due to hyperplasia of the posterior lobe and that the increased sugar tolerance which may develop later is due to the hypoplasia of the posterior lobe, which he believes not infrequently occurs late in the course of the disease. Accepting the theory that Fröhlich's syndrome is due to hypoplasia of the posterior lobe, he believes that a factor in the adiposity is the increased sugar tolerance. In other words, he considers the posterior lobe as playing an important role in sugar metabolism. When overactive, lessened tolerance occurs, and when underactive, an increase of tolerance above the normal. He reports an invariable glycosuria in rabbits after intravenous injection of extracts from the posterior lobe. It may be said that these views of Cushing have not been generally confirmed by other observers. During the past year Forschbach and Severin have studied the sugar tolerance in acromegaly, Fröhlich's syndrome, and in hypophyseal tumors without developmental disturbances. Their results show there is a lack of constancy of the sugar tolerance in each of these conditions. Two patients with acromegaly, one of fifteen years' duration, showed marked increased sugar tolerance, another of twelve years' duration a lessened tolerance; two Fröhlich syndromes had a normal tolerance, and 3 cases of hypophyseal tumors, without developmental disturbance, an increased tolerance. Bernstein reports two Fröhlich syndromes with normal sugar tolerance and two others with increased sugar tolerance. Recently, Woodyatt, with his new method, studied the sugar tolerance in a

patient of mine with diabetes insipidus and Fröhlich's syndrome, of eight years' duration and did not detect any variation from the normal. Believing that this sugar tolerance was due to a hormone arising in the posterior lobe, Weed, Cushing, and Jacobson after sectioning the cord and stimulating the hypophysis were able to produce glycosuria. Keeton and Becht have repeated this experiment, but instead of cutting the cord have severed the splanchnics and have been unable to cause a hyperglycemia by stimulating the hypophysis. They did show, however, that electrical stimulation of the hypophysis in dogs gave rise to a hyperglycemia, while this did not occur in stimulation of the adjacent structures.

Experimental efforts to produce glycosuria in animals by injecting extracts of the hypophysis give conflicting results; Borchard obtained positive results in 28 out of 35 rabbits and 5 out of 7 dogs. Pal's results were negative, Franchini with 22 rabbits had 2 positive results. Lewis and Miller injected 30 rabbits, 15 with anterior and the same number with positive lobe extracts, and only 1 animal in each series developed glycosuria. Very recently Bernstein reported that he was unable to produce glycosuria by extracts of either the anterior or posterior lobe.

From these conflicting results it is apparently impossible to determine the role, if any, of the hypophysis in sugar metabolism. The readiness with which glycosuria appears after a multitude of disturbance to the brain adds to the confusion. Falta reports transitory glycosuria in 20.8 per cent. of skull fractures of convexity and 23.8 per cent. of basal fractures, and in 9.3 per cent. of severe head injuries without fracture. Glycosuria is common in tumors in various parts of the brain, and especially of the floor of the fourth ventricle. The readiness with which glycosuria appears in animals after anesthesia renders it difficult to draw conclusions as to the cause of glycosuria after operative measures in the hypophysis.

Galactogogue Action. Ott, in 1910, discovered the galactogogue action of the hypophyseal extract. He found that when given intravenously to goats or cats there appears within one-half minute a marked increase in the amount of milk excreted from the breast. When given subcutaneously to lactating women similar results are obtained. The milk after the administration of the hypophyseal extract is especially rich in fat. This might appear to have some practical value in increasing and improving the quality of milk output. It has been shown, however, that in the second milking after the injection there is a reduction below normal in the quantity of milk, and the percentage of fat is decreased so that the total output and fat content in the twenty-four hours is not increased. Simpson and Hill have shown that an immunity is rapidly acquired in goats after its prolonged use, the effect on the quantity and fat content becoming much less apparent. This galactogogue sub-

stance is present only in the posterior lobe. Herring has made the interesting observation that the anterior lobe of the hypophysis of some reptiles contains a galactogogue agent. The galactogogue action of the extract does not run parallel to its vascular action, and the belief is that it acts directly on the secretory cells of the mammary gland.

The hypophysis during pregnancy undergoes a hypertrophy and hyperplasia. These changes, however, are apparently confined to the anterior lobe, the chromophobe cells being changed into a special cell of pregnancy, which after confinement reverts back again to the normal chromophobe cell. The posterior lobe, which is the source of the galactogogenic substance, does not, as far as is known, undergo any change either during pregnancy or lactation.

Osteomalacia. The etiology of osteomalacia is still undetermined. It has been ascribed by different observers to disturbed function of the ovaries, suprarenals, parathyroid, and hypophysis. These results are so conflicting that it is impossible to say whether any of the ductless glands are concerned in its development. Bossi, Christolette and others have reported improvement after the use of adrenalin, and Bab has reported beneficial results after the use of pituitrin, and Pal after feeding with extracts of the anterior lobe.

Use in Cardiovascular Condition. Pituitrin when given intravenously, much less constantly when given intramuscularly, causes a gradual and rather prolonged rise in blood-pressure with slight slowing of the heart. The rise in pressure is due to vascular constriction, the drug acting directly upon the musculature in the vessel wall, resembling in this respect barium chloride. This slowing of the heart is due chiefly to stimulation of the cardio-inhibitory mechanism and partly to direct effect on the heart muscle. It is generally thought that, as a result of direct action on the muscle, the heart's contractions are strengthened. Wiggers, however, believes its effect on the heart is depressive at least in the majority of instances.

Judging from the literature, hypophyseal extracts have not been used extensively in cardiac condition. A few references have been made to their value in the cardiovascular disturbances in the acute infection. More clinical observations must be made, however, before it can be determined whether pituitrin is of real value in these conditions.

Action on the Uterine Musculature. Extracts of the posterior lobe of the hypophysis stimulates uterine contraction by its direct action on the unstriated muscle. Apparently the reaction of the uterus varies somewhat in different animals. In guinea-pigs it has a marked action on both the pregnant and virgin uterus; in rabbits only in the pregnant uterus. During the past four years there has developed a very extensive literature on the value of

pituitrin and allied preparation in stimulating the uterus during labor. The results, on the whole, are quite favorable, and, provided a proper selection of cases is made, is largely free from danger. It should only be used in the second stage of labor when the os is well dilated. In the earlier stages of pregnancy it is contraindicated, as it may excite uterine contractions without dilatation of the os. When the os is dilatated and uterine contractions are feeble, 1 to 2 c.c. of pituitrin intramuscularly may be of considerable value. The pituitrin may also be of value in postpartum hemorrhage.

Effect of Intestinal Peristalsis. Bayer and Peter have shown that the posterior lobe extracts cause first a lessening of the tonus and peristaltic action of the intestine, soon followed, however, by increased tonus and greatly increased peristalsis. After the use of the extract, peristalsis may be excited in an isolated piece of intestine in which all rhythmical contraction had ceased. Klotz and others have recommended extracts of the posterior lobe for postoperative peritonitis. Here absence of vascular tone in the splanchnics, of toxic origin, is largely responsible for the distention. The extract by acting directly on the musculature of the vessel wall, and at the same time stimulating intestinal peristalsis, should tend to relieve the condition. He reports decidedly beneficial results in twenty patients. He used pituitrin intravenously, diluting it with normal salt solution and injecting very slowly. He has also used, with beneficial results, intramuscular injections of 2 c.c. Klotz and others have also used pituitrin with apparent good results in the treatment of mild intestinal obstruction and in postoperative intestinal stasis. During the past two years I have used pituitrin, 1 c.c. intramuscularly, in the treatment of the abdominal distention complicating pneumonia, but have never observed any beneficial results. Perhaps if used intravenously desirable action might be obtained.

Action on the Bladder. Frankl Hochwart and Fröhlich, in 1910, reported marked increase in bladder contraction in cats after the use of pituitrin. Here again it affects directly the unstriated muscle. During the past few years several favorable reports have appeared on its value in causing spontaneous empyting of the bladder and thus avoiding catheterization after confinement (Cahor, Schirmer), and following operation on the pelvic organs (Jasches). The usual dose, 1 to 2 c.c., is given intramuscularly.

Control of Hemorrhage. On account of its action on unstriated muscle we can readily see how pituitrin might be of value in uterine hemorrhage of certain character, especially postpartum hemorrhage. It is more difficult to explain why it should have an effect on hemorrhage elsewhere. It is true it acts as a vasoconstrictor, and agents of this character do not necessarily affect all vessels in the same manner. Adrenalin, for instance, is a powerful vasoconstrictor, but dilates the coronary arteries. A vasoconstrictor

which affected certain bloodvessels without raising the general blood-pressure might have a hemostatic effect in organs where vasoconstriction occurred. As a rule, however, vasoconstrictors by raising blood-pressure interfere with the fixation of the clot, and are, therefore, contraindicated in hemorrhage. Celilli, in 1914, recommended posterior lobe extracts, given subcutaneously for the control of hemorrhage in nasal and throat operation. Since then there has been confirmation of his results. Rist, in 1913, and later Minet and Martin recommended this agent for the treatment of hemorrhage in pulmonary tuberculosis. The former gave 0.5 c.c. intravenously. It is a question whether with a severely ill tuberculous patient it would be advisable to give the drug intravenously on account of the danger of exciting vomiting and vertigo. Kahn and Gordon, who have studied the effect of pituitrin on blood coagulation, report reduction of the coagulation time by half; in this respect it behaves like adrenalin (von den Velden). If time should show that pituitrin acts as a hemostatic it will probably be explained on its effect on coagulation rather than its vasoconstrictor action.

This concludes the therapeutic application of hypophyseal extracts. It will be noted that these results were obtained only with extracts from the posterior lobe. They must be given subcutaneously, intramuscularly, or intravenously to obtain any action. By mouth, like adrenalin, they are inactive. Perhaps time will show that the anterior lobe may be of value in stimulating growth and sexual activity, but experimental and clinical evidence of this action is still lacking.

In closing, mention should be made of the use of posterior lobe extracts in the treatment of bronchial asthma. On account of pituitrin having an effect on blood-pressure somewhat resembling adrenalin, several publications have appeared recommending its use in bronchial asthma. This is apparently wrong. Pal, Fröhlich and Pick, Baehr and Pick, and others have shown that pituitrin produces bronchial spasm, while the relief given by adrenalin, is due to its power to dilate the bronchi. Baehr and Pick have also shown that when combined with adrenalin the pituitrin action on the bronchi is inhibited by the adrenalin. This probably accounts for the beneficial action of a proprietary preparation containing pituitrin and adrenalin recommended for the treatment of asthma.

As a complete bibliography may be found in Biedl's *Innere Sekretion*, 1913, 2d edition, only a few of the more recent references will be given.

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THE VALUE OF THE AMBARD QUOTIENT IN THE ESTIMATION OF RENAL FUNCTION.

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In this study are reported the results obtained from the determination of Ambard's quotient of renal efficiency (as modified by McLean) in a series of clinical cases with and without nephritis. Ambard's quotient was the outcome of a series of studies beginning with that of Ambard and Papin,[1] in 1909, upon the laws governing the concentration of urea in urine. Previous workers had noted the difficulty of securing a constant urea concentration in the urine of either man or animals even on carefully controlled diets. Ambard and Papin found, however, that in the dog an exclusively meat diet with as much water as the animal desires produces a urine of remarkably uniform urea concentration. This concentration of urea under these conditions is independent of the protein content of the diet and is the maximal urinary urea concentration for that animal. Any factor which unduly increases the animal's thirst, such as the feeding of bread or of salt, a diarrhea, or an inadequate supply of food, will, if water is freely available, disturb this relation in the urea excretion and lower the concentration of the urea in the urine. These authors further observed, however, that the kidney can eliminate a much larger amount of urea in a unit time if the

[1] Étude sur les concentrations urinarires, Arch. internat. de physiol., 1909, viii, 437.

secretion be accomplished at a lower concentration. When the renal parenchyma was sufficiently reduced experimentally the animal could eliminate urea only at a lower concentration. At this lower concentration, however, a very large amount of urea could be excreted as the result of a polyuria, only following the stimulation from an accumulation of urea in the blood. Ambard[2] showed that both in the dog and in man, if a constancy of the urea concentration in the urine is maintained, the square root of the urea eliminated in the urine during any unit of time is closely proportional to the concentration of the urea in the blood in any given individual, and that this law (Ambard's first law) holds for nephritis as well as for the normal kidney. The unit of time used for measuring the urea excretion must, however, be short (about an hour or less), since the continual variations in both the rate of urea excretion and the concentration of the blood urea will otherwise cause apparent discrepancies in their interrelations. Variations in the concentration of the urea in the urine alter, however, the relation between the rate of urea excretion and the urea concentration of the blood. An effort was made by Ambard[3] to define mathematically the effect of this factor of concentration. To do so, however, was not easy, because of the extreme difficulty of obtaining subjects in which, with varying urinary urea concentration, the blood urea concentration remained constant. After many examinations, two subjects in which these conditions were realized were observed, and from them Ambard concluded (second law) that if the blood urea remains at a constant concentration, the rate of urea excretion is inversely proportional to the square root of the urea concentration in the urine. The validity of this second law was by no means so well established by Ambard's work as was his first. On the basis of these two laws, Ambard and Weill[4] developed a formula into which was introduced with these two factors, in the relations stated, an additional factor designed to compensate for the variations in weight between different individuals arbitrarily selecting 70 kilos as the standard weight. They also adopted in this formula 25 gms. of urea per liter as the standard concentration of urea in the urine. In its complete form, Ambard's quotient is as follows:

$$\text{Constant} = \frac{\text{Ur.}^2}{\text{D} \times \frac{70}{\text{wt.}} \times \frac{\sqrt{\text{c}}}{25}}$$

Ur. — gm. of urea per liter of blood.
D. — gm. of urea excreted in twenty-four hours.
Wt. — wt. of individual in kilos.
c. — gm. of urea per liter of urine.

[2] Rapports entre le taux de l'urée dans le sang et l'elimination de l'urée dans l'urine, Comp. rend. Soc. de biol., 1910, lxix, 411.

[3] Rapports de la quantité et du taux de l'urée dans l'urine, la concentration de l'urée du sang étant constante, ibid, 506.

[4] Les lois numériques de la secretion rénale de l'urée et du chlorure de sodium, Jour. de physiol. et de path. gén., 1912, xiv, 753.

For the sake of simplifying the calculation, and in order to make the quotient rise and fall with the renal efficiency instead of rising as the renal efficiency falls, and *vice versa*, as is the case with Ambard and Weill's constant, McLean[5] has transposed the original formula without altering its essential principle, so that it stands as follows:

$$\text{Index} = \frac{\text{Gm. urea per 24 hours} \times \sqrt{\text{gms. urea per liter urine}} \times 8.96}{\text{Wt. in kilos} \times (\text{gm. urea per liter of blood})^2}.$$

When Ambard and Weill's quotient = 0.080, the standard normal, McLean's index = 100. According to McLean this index should be above 80 when renal function is normal, and indices below 80 indicate more or less impairment of renal function.

It must be remembered that Ambard's formula is constructed on a purely empirical basis. The particular functions, the square and square root, being chosen not on any logical grounds but merely because, in a number of instances, under certain conditions, the use of these functions gave calculated results agreeing with the observed findings. Even though each of Ambard's laws hold independently under the partially constant conditions of the original studies, it might be questioned whether the combination of these two laws as expressed in their formula would necessarily hold under varying conditions. That their formula does frequently accord with the observed facts has been shown by Ambard and Weill, by McLean and others. On the other hand, McLean, using his modification, sometimes obtains indices in normal individuals exhibiting the wide range of from 80 to 250. Addis and Watanable[6] conclude that the rate of urea excretion in man varies under physiological conditions, and that these variations cannot be completely explained by the variations in the amount of urea in the blood and urine. Pepper and Austin,[7] in dogs (using, however, total nitrogen instead of urea), found enormous variations in the quotient in different animals and in the same animals under different conditions. The question probably arises, therefore, as to whether Ambard and Weill's formula or its modification is the precise expression of the fundamental physiological law that governs the relation between the concentration of urea in the blood and in the urine and the rate of urea excretion, or whether it is merely a crude approximation to the actual quantitative relation, a sort of diagram that indicates the direction in which changes in one of the factors concerned will influence the others. This question can best be answered by an

[5] The Numerical Laws Governing the Rate of Excretion of Urea and Chlorides in Man, Jour. Exper. Med., 1915, xxii, 212.

[6] Rate of Urea Excretion; a Criticism of Ambard's and Weill's Law of Urea Excretion, Jour. Biol. Chem., 1916, xxiv, 203.

[7] Experimental Studies of Urinary and Blood Nitrogen Curves after Feeding, Jour. Biol. Chem., 1915, xxii, 81.

investigation of the quotients obtained in the same normal individual at different times under different conditions and by a comparison of the quotients obtained from different normal individuals. Only if these quotients consistently approximate a constant can we accept the formula as representing anything more significant than a sort of diagram of these relations.

A study of the quotient derived by applying Ambard's formula as modified by McLean to a number of individuals with presumably normal kidneys shows at once that the quotient obtained is anything but constant.

CHART I.—CASES WITH PRESUMABLY NORMAL KIDNEYS.

No.	Name.	Date.	Age.	Sex.	Diagnosis.	Urine urea per 24 hours.	Urine urea per liter.	Blood urea per liter.	Weight (kilo).	Index.	Blood-pressure.
1	Kelly	Jan. 17, 1916	37	M	Perihepatitis; pleurisy	17.90	9.23	.23	70	145	
		Jan. 25, 1916				20.98	11.90	.30	72	113	
		Jan. 21, 1916				20.08	5.22	.22	70	116	
2	Wa.	Jan. 5, 1916	24	M	Gastric neurosis; constipation	20.62	10.31	.19	56	280	90–68
		Jan. 8, 1916				27.67	2.82	.24	54	132	
		Jan. 10, 1916				20.20	4.80	.16	54	267	
3	VanS.	Feb. 1, 1916	29	M	Endothelioma of lymph nodes	20.9	12.0	.21	61	242	126–76
		Feb. 5, 1916				28.27	12.61	.24	61	255	
4	Ma.	Feb. 1, 1916	46	M	Angina pectoris	17.18	7.68	.21	75	128	104–70
		Feb. 8, 1916				29.46	6.71	.27	75	124	
		Feb. 15, 1916				16.78	8.16	.24	75	99	
5	Ki.	Jan. 27, 1916	..	..	Epilepsy	23.04	7.68	.23	70	153	
		Jan. 21, 1916				23.22	5.53	.33	70	64	
6	Li.	Nov. 8, 1915	50	M	Sciatica	11.46	17.40	.19	75	147	115–85
		Nov. 18, 1915				9.18	22.97	.22	77	79	112–74
		Nov. 30, 1915				24.25	26.25	.25	77	219	112–68
7	Gr.	Dec. 20, 1915	26	M	Bronchial asthma: subacute bronchitis	34.80	14.04	.27	72	222	
		Dec. 23, 1915				31.78	10.45	.24	71	224	
8	Em.	Nov. 21, 1915	42	M	Syphilitic hepatitis	24.52	26.7	.30	75	185	117–65
9	Mi.	Jan. 5, 1916	18	M	Chronic arthritis; mitral regurgitation with compensation	9.60	20.87	.22	63	124	122–70
10	At.	Jan. 5, 1916	22	M	Pulmonary infarction; subacute mitral and aortic regurgitation with compensation	14.16	19.15	.31	58	96	116–54
11	Ka.	Feb. 29, 1916	63	M	Headache	14.66	22.88	.31	54	120	115–75

In this study, which was made on patients in the medical wards of the University Hospital, periods of 72 minutes were employed (or in a few instances slightly larger periods up to 160 minutes) and the blood withdrawn from an arm vein 36 minutes after the period began. The urea was determined by the urease method described by Van Slyke and Cullen.[8]

The cases may be divided into three groups: First, cases in which there is no clinical or laboratory evidence of nephritis, nor of marked cardiovascular disease, nor of cardiac decompensation; the findings in these cases are tabulated in Chart I. Second, cases

[8] A Permanent Preparation of Urease and its Use in the Determination of Urea, Jour. Biol. Chem., 1914, xix, 211.

CHART II.—CASES WITH NEPHRITIS.

No.	Name.	Date.	Age.	Sex.	Diagnosis.	Urine urea per 24 hrs.	Urine urea per liter.	Blood urea per liter.	Weight.	Index.	Blood-pressure.	Eye-grounds.
1	Br.	Feb. 25, 1916	44	M	Advanced glomerulonephritis; cardiac decompensation	12.17	10.35	1.43	77	2	180 to 140	Sclerosis; retinitis.
		Mar. 4, 1916				10.83	8.20	1.05	80	3		
		Mar. 8, 1916				10.51	5.88	1.09	80	2		
2	McC.	Nov. 30, 1915	53	M	Advanced chronic nephritis	27.15	8.58	.94	66	12	210 to 150	Retinal exudate and edema.
		Dec. 15, 1915				20.93	17.16	1.14	66	9		
		Dec. 17, 1915				33.00	13.85	.98	64	18		
		Dec. 20, 1915				15.25	13.45	1.17	64	5.7		
3	Jo.	Nov. 29, 1915	35	M	Chronic glomerulonephritis	20.73	19.20	.75	62	23	180 to 112	
		Dec. 31, 1915				9.78	13.59	.51	62	20		
4	St.	Nov. 4, 1915	24	M	Advanced glomerulonephritis	18.02	4.00	.45	64	25	172 to 126	Neuroretinitis; exudate and hemorrhage.
		Nov. 15, 1915				18.01	4.02	.42	59	27		
		Nov. 29, 1915				16.23	2.75	.24	61	23		
		Dec. 3, 1915				23.75	5.11	.30	60	140		
5	O'D.	Apr. 17, 1916	39	F	Advanced glomerulonephritis	21.02	8.08	1.93	112	1.3	250 to 160	Marked neuroretinitis.
6	Wa.	Feb. 1, 1916	24	M	Chronic endocarditis; chronic nephritis; intermediate	55.4	16.10	.90	62	40	160 to 120	
7	An.	Jan. 5, 1916	47	F	Advanced glomerulonephritis	8.07	12.60	.83	68	5	272 to 141	Sclerosis; retinitis.
8	Ba.	Mar. 6, 1916	15	M	Glomerulonephritis; intermediate	16.38	13.76	.49	47	60	165 to 115	Negative.
9	Hi.	Nov. 27, 1915	55	M	Chronic glomerulonephritis	20.23	26.63	.48	64	64	210 to 110	
10	Ya.	Mar. 11, 1916	26	F	Chronic nephritis; intermediate	16.5	9.16	.46	47	44	140 to 110	Negative.
11	Mo.	Feb. 8, 1916	45	M	Glomerulonephritis; intermediate	31.2	21.42	.39	83	103	185 to 135	Neuroretinitis.
12	Ch.	Mar. 9, 1916	36	M	Glomerulonephritis; intermediate	15.35	15.75	.37	67	61	176 to 110	Sclerosis.
13	Dav.	Apr. 17, 1916	21	F	Chronic degenerative nephritis	13.07	13.35	.37	58	59	160 to 130	Negative.
14	Wh.	Feb. 2, 1916	24	F	Glomerulonephritis; intermediate	19.18	2.93	.31	49	62	198 to 175	Early retinitis.

with definite evidence of more or less severe nephritis; tabulated in Chart II. Third, a few cases in which there is no definite nephritis; but in which there is more or less vascular disease or cardiac decompensation or both; tabulated in Chart III.

CHART III.—CASES WITH VASCULAR DISEASE.

No.	Name.	Date.	Age.	Sex.	Diagnosis.	Urine urea per 24 hours.	Urine urea per liter.	Blood urea per liter.	Weight (kilo).	Index.	Blood-pressure.
1	Bo.	Nov. 22, 1915	50	F	Sclerotic hypertension; cardiac decompensation	32.76	11.7	.34	56	15	200–110
2	Ro.	Feb. 29, 1916	57	M	Arteriosclerosis	9.2	7.1	.31	60	38	142– 85
3	Hur.	Nov. 8, 1915	63	M	Myocardial weakness	16.45	2.94	.30	84	33	122– 83
		Nov. 18, 1915				11.25	4.50	.24	85	43	145– 98
4	Da.	Feb. 27, 1916	59	M	Sclerotic hypertension	17.41	6.00	.37	54	47	170– 12
5	Ki.	Nov. 2, 1915	36	M	Chronic myocarditis	22.07	4.32	.28	79	64	121– 72
		Nov. 16, 1915				10.72	22.33	.38	79	36	
		Nov. 16, 1915				26.55	14.62	.30	..	176	

CHART IV.

Name.	Diagnosis.	Date.	Urine urea per liter.	D. Urine urea per 24 hours.	Ur. Blood urea per liter.	$\frac{Ur}{\sqrt{D}}$
Van S.	Endothelioma; lymph nodes	Feb. 1, 1916	12.00	20.90	.21	.045
		Feb. 5, 1916	12.61	28.27	.24	.045
Ma.	Angina pectoris (very mild)	Feb. 1, 1916	7.68	17.18	.21	.051
		Feb. 8, 1916	6.71	29.46	.27	.050
		Feb. 15, 1916	8.16	16.78	.24	.058
McC.	Advanced nephritis	Dec. 17, 1915	13.85	33.00	.98	.171
		Dec. 20, 1915	13.45	15.25	1.17	.300
St.	Advanced nephritis	Nov. 4, 1915	4.00	18.02	.45	.106
		Nov. 15, 1915	4.02	18.01	.42	.099
		Dec. 3, 1915	5.11	23.70	.30	.062

			Blood urea per liter.	D. Urine urea per 24 hours.	C. Urine urea per liter.	$D \times \sqrt{C}$.
Ke.	Perihepatitis	Jan. 17, 1916	.23	17.90	9.23	54
		Jan. 21, 1916	.22	20.08	5.22	46

Inspection of the cases tabulated in Chart I, cases in which presumably the kidneys are normal, shows the wide variation that is observed in the index in the same individual on different occasions and in different individuals. We may profitably examine certain of these cases from another point of view. If those instances of repeated examinations on the same individual where the urea concentration in the urine was approximately constant be chosen we find five examinations (see Chart IV) on two normal individuals. If to the data of these examinations Ambard's first law be applied

it will be found to be confirmed in the first case, the ratio of $\frac{Ur}{\sqrt{D}}$ being constant in the two examinations on this case and also in the first two examinations of the second case. Among the nephritic cases five examinations from two cases exhibit approximately constant urinary urea concentration, but Ambard's first law does not hold in these cases. This is, perhaps, due to progression of the renal impairment in the first case and amelioration in the second.

If we select from our data those non-nephritic cases with repeated examinations showing constant blood urea concentration for the purpose of verifying Ambard's second law we can find only one case (see Chart IV). In this case Ambard's second law is but poorly supported. This finding is quite in harmony with the results previously quoted from Pepper and Austin; it is when there is variation in the urinary urea concentration that Ambard's formula most frequently gives unsatisfactory results. However, since variability in the concentration of urea in the urine is the rule and not the exception, this defect may seriously impair the value of Ambard's formula as a gauge of renal function under ordinary clinical conditions. The variability which we have found in the constant at repeated examinations of the same non-nephritic case or in comparing with each other one group of non-nephritic cases leads us to conclude that Ambard's formula is not a mathematically accurate expression of the behavior of renal function as regards urea excretion, but that it is merely a crude diagrammatic indication of certain relations between blood urea and urea excretion and urinary urea concentration.

The question must arise, however, whether Ambard's quotient or its modification, in spite of this objection that may be urged against it, is of value clinically as an index of renal function. If we can demonstrate that the quotient gives with reasonable constancy, information evidently more consistent with the clinical condition and subsequent course of the patient than does the careful inspection of those factors separately that go to make the quotient, we might well employ the quotient for diagnostic and prognostic purposes. On the other hand the determination of the index, because of the necessity for great accuracy in collection of the urine, is a much more difficult procedure to carry out than is the simple estimation of the blood urea, and more important still there are possibilities of undetected errors occurring through the loss of a small quantity of urine. Hence, unless some definite advantage can be urged in favor of the quotient as compared with the simple blood urea considered with due regard to the character of the urinary excretion, the latter would appear to be the safer criterion in clinical diagnosis and prognosis.

Inspection of our results would lead us to conclude that if we are to accept McLean's normal blood urea figures, 0.20 to 0.50 gms. per

liter as correct, then the index is a more delicate measure of renal impairment than is the blood urea.

In our nephritic group, 10 out of 23 examinations show a blood urea within McLean's normal figures and 21 out of 23 give figures for the index below 80, which, according to McLean, indicates impairment of renal function. The clinical picture would lead us to suspect impairment of renal function in those cases. If, however, we accept Tileston's and Comfort's[9] figures for blood urea, 0.35 gms. per liter, or Folin and Denis's[10] urea figures, 0.23 and 0.28 gm. per liter as normal, then in out studies the index no longer possesses any advantages over the blood urea.

Inspection of Chart I will show that we have never found a blood urea in a normal or non-nephritic individual above 0.35 gm. per liter under ordinary conditions, and we have, accordingly, accepted this figure as the upper normal limit, which is in accord with the views of Tileston and Comfort. Accepting 0.35 gm. per liter as the upper limit of normal, then it is readily seen that in our nephritic cases blood urea alone gave as satisfactory evidence of impairment of function, as did the index except in the third examination of St. and in the case of Wh.

In the case of Wh. and the third examination of St. the index gave information which the blood urea alone would have failed to show.

Inspection of Chart III shows that in cases in which in all probability the only impairment in renal function is the result of arteriosclerotic changes or of renal passive congestion, the index may show pronounced depression while the blood urea remains within normal limits. There is evidence to suggest, therefore, that the index is at least in certain cases a more delicate gauge of renal impairment than is the blood urea. It is at least possible, however, and indeed highly probable, that for clinical purposes of diagnosis and prognosis these cases present rather an argument against the use of the index and for the blood urea than the reverse. It is in part because the estimation of the blood urea often helps to distinguish true nephritis from arteriosclerotic lesions, or from congestion of the kidney, that it is of value in these cases. Clearly for this purpose the index would be of less value, being too sensitive and too readily reduced by arteriosclerotic condition and by passive congestion as well as by nephritis.

On examination of Chart III, which consists of frank cases of nephritis, one fails to see the marked variability in the index in individuals in whom more than one examination has been made that was noted in the non-nephritic cases. This tendency to constancy of the index in cases of nephritis with impaired function has also been emphasized by McLean.

[9] The Total Non-protein Nitrogen and the Urea of the Blood in Health and Disease as Estimated by Folin's Method, Arch. Int. Med., 1914, xiv, 620.

[10] On Uric Acid, Urea, and Total Non-protein Nitrogen in Human Blood, Jour. Biol. Chem., 1913, xiv, 29.

The patient St. shows marked rise of the index on the fourth examination, due to the elimination of a urine of higher urea concentration and to a higher urea output which have most probably been caused by large doses of infusion of digitalis which he received between the time of the second and third examination.

Finally, it seems possible that in conditions in which there is either an extremely high nitrogenous intake or in which there is very rapid tissue catabolism, the blood urea may be raised above 0.35 gm. per liter, although renal function is quite normal, and that this may be accompanied by an increased rate of urea elimination in the urine with a normal index. In such cases the index would be a better gauge of the state of renal efficiency than would the blood urea alone. McLean has induced just such a condition by the administration of urea to normal individuals. Under ordinary circumstances, however, such conditions do not obtain, and our conclusion would be that, as a rule, the blood urea alone is a better guide in ordinary clinical diagnosis and prognosis than is the index.

CONCLUSIONS. 1. The Ambard formula in its original form or as modified by McLean does not express precisely the law of renal function with respect to the elimination of urea, and this is particularly true as regards the effect of urinary urea concentration.

2. The upper limit of blood urea in non-nephritic and normal individuals under ordinary conditions of diet and life is about 0.35 gm. urea per liter of blood. Figures higher than this are, under ordinary conditions of diet, to be considered evidence of impaired renal function.

3. Using McLean's modification of Ambard's formula, it was found that in the great majority of nephritic cases a lowering of the index was accompanied by an elevation of the blood urea above normal limits, 0.35 gm. per liter, and that the index afforded no information of diagnostic or prognostic value that could not be as readily deduced from the blood urea alone.

4. In certain cases the index was found to be lowered when the blood urea was within normal limits. This was especially true in arteriosclerotic cases and in cases with cardiac decompensation, which probably detracts from the clinical value of the index as compared with that of the blood urea rather than the reverse, since it is of importance to distinguish between cases of vascular and renal character.

5. In the determination of the index there is a possibility of error arising from undetected incomplete collection of the urine, which cannot occur in the simple blood urea estimation.

6. The urea index estimated repeatedly in the same individual exhibits wider variations in the normal or non-nephritic individual than in the nephritic.

7. For purposes of ordinary clinical diagnosis and prognosis the estimation of blood urea is a more reliable and more useful guide than is the urea index or the Ambard quotient.

THE EXPECTORANT ACTION OF AMMONIUM CHLORIDE.[1]

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Ammonium chloride is used so extensively in the treatment of respiratory affections that it is important to determine whether it does or does not possess an expectorant action.

All of the text-books on pharmacology which I have consulted regard ammonium chloride as an expectorant. Cushny, however, merely says that "ammonium chloride is generally credited with acting on the secretion of the bronchial mucous membrane, which it is said to render more fluid and less tenacious and at the same time to increase considerably." The majority of text-books on therapeutics recommend ammonium chloride in the treatment of respiratory diseases.

In the discussion of Dr. Miller's[2] paper on "The Clinical Value of Expectorants," read before the Association of American Physicians, Dr. Meltzer said "ammonium chloride is, I believe, a reliable remedy for increasing secretion and expectoration." Other speakers expressed themselves in similar vein.

Yet on the basis of a few experiments upon lower animals in which important factors were not controlled, it has been denied that ammonium chloride in the usual therapeutic doses acts as an expectorant upon patients suffering from bronchitis.

In view of the doubt which has thus been created, I decided to reinvestigate the action of ammonium chloride upon the bronchial secretion in man. Patients with acute or chronic bronchitis were selected as subjects for the experiment. The objections which have been brought against the validity of such experiments do not appear to me to be fundamental. They are based upon the assumption that to act as an expectorant a drug must increase the total quantity of secretion within arbitrarily fixed periods. The generally accepted definition of an expectorant is a drug which facilitiates the expulsion of mucus from the respiratory passages. Under this definition a drug may soften and release mucus from the walls of the bronchi without increasing the quantity in twenty-four hours. In fact, if we assume a healing effect of the drug upon the inflamed mucous membrane, as is generally done, the amount of secretion for the twenty-four hours may at times be actually diminished. Yet this

[1] Presented before the Association of American Physicians, Washington, May 11, 1916.

[2] Tr. Assn. Amer. Phys., 1914, xxix, 139.

does not invalidate the conclusion that the drug is an expectorant in the sense that it makes expectoration easier.

EXPERIMENTS ON LABORATORY ANIMALS. The experiments on the action of ammonium chloride upon the bronchial secretion of laboratory animals may be summarized as follows:

They were carried out on dogs and cats. The preliminary operations were done under chloroform or ether, or both. The trachea was severed in all experiments; in most of them the mucous membrane was exposed for direct observation. The anesthesia was prolonged by chloral, chloretone, or urethane.

The conclusions concerning the expectorant action of the drugs studied (ammonium chloride, ammonium carbonate, antimony, squills, senega, apomorphin, ipecacuanha, and pilocarpin) were based either upon inspection of the mucous membrane or the weight of a piece of filter paper before and after it had been placed in contact with the mucous membrane, or by the amount of secretion which could be led off from the trachea through a tube. When there was no visible increase in the secretion and no increase in the weight of the filter paper the conclusion was drawn that the drug under investigation did not possess expectorant properties.

All of these experiments are open to objections which vitiate the conclusions drawn from them. The objections are as follows:

No proof is offered that the anesthetics employed (chloral, chloretane, urethane) were without influence upon the bronchial secretion.

The evaporation of water from the exposed mucous membrane of the trachea is left entirely out of consideration. The control of this factor is of the highest importance.

The assumption is made that all expectorants produce a visible increase in the bronchial secretion under the conditions of the experiments.

Until these objections have been met the negative results obtained cannot be considered as conclusive.

One of the arguments advanced to disprove the expectorant action of ammonium chloride is that a large proportion of the drug is converted to urea in the liver—according to Biedl and Winterberg,[3] from one-half to four-fifths—and that with the usual therapeutic doses the amount reaching the general circulation would be too small to affect the viscosity of the bronchial secretion.

More recent experiments, however, do not support the observations of Biedl and Winterberg. Wolf and Osterberg[4] studied the influence of ammonium chloride upon the ammonia nitrogen curve in the urine. The experiment was performed upon one of the authors. The normal ammonia nitrogen excretion was first deter-

[3] Arch. f. d. ges. Physiol., 1901–02, lxxxviii, 140.
[4] Biochem. Ztschr., 1912, xl, 193, 234.

mined and then 5 grams of ammonium chloride was taken in one dose. The result was as follows:

Average normal output of ammonia nitrogen = 0.366 gm.	0.732 gm.
Ammonium nitrogen in two days after ammonium chloride =	1.537 "
Difference	0.805 "
Nitrogen in 5 gms. ammonia chloride	1.308 "

This experiment shows that 52.5 per cent. of the ammonium chloride was eliminated by the kidneys alone in two days. Of special interest is the fact that the ammonia nitrogen curve in the urine reached its highest point within two hours after the ammonium chloride was taken. The urea excretion (expressed in terms of per cent. of total nitrogen) fell from the daily normal of 79.50 per cent. to 75.40 per cent. on the day the ammonium chloride was taken. The ammonia nitrogen in the urine rose from 4.10 per cent. to 10.24 per cent. on the same day.

These results, together with the progressive increase in the ammonia nitrogen content of the sputum, make it clear that in man little if any ammonium chloride is changed to urea in the liver.

THE PLAN OF EXPERIMENT. The plan of experiment which I followed was: First, examination of the sputum of patients suffering from acute or chronic bronchitis for the ammonia nitrogen content, and second, observations upon the subjective symptoms referable to the respiratory passages following the administration of ammonium chloride.

If it can be proved that ammonium chloride is excreted as such, in appreciable quantities, by the bronchial mucous membrane, and if at the same time the secretion is more easily expelled, I believe that the expectorant action of the drug will thereby be established.

Seven persons, including Dr. B. F. Weems, house physician, a nurse in training, and myself were used as subjects of the experiment. All were suffering from acute or chronic bronchitis.

The sputum was collected before the administration of the ammonium chloride was begun and at various times thereafter. It was put at once into bottles containing chloroform and placed in an ice-box to prevent decomposition.

Subjective observations were made only by Dr. Weems and myself.

The doses of ammonium chloride varied from ½ grain every two hours to 5 grains every two hours.

THE AMMONIA NITROGEN IN THE SPUTUM.[5] Standard solutions were prepared containing 0.01, 0.02, 0.025, 0.03, 0.035, 0.04, 0.045,

[5] I wish to express my appreciation of the kindness of Dr. Stanley Benedict in making the chemical tests.

0.05, 0.06, 0.07, 0.08, 0.09, and 0.10 mgm. of ammonia nitrogen in 5 c.c.

A sample of sputum from each patient as centrifuged and 1 c.c. of clear fluid was measured into a test-tube; this was diluted to 5 c.c. with water, treated with 10 drops of Nessler's reagent, and compared with the above standards (treated with an equal amount of Nessler's solution).

Typical results follow:

N. W. A. The ammonium chloride was taken in ½-grain doses every two hours.

Before taking	0.02
After 10 grains	0.015
" 30 "	0.035
" 85 "	0.050

Davey. The ammonium chloride was taken in 5-grain doses every two hours.

Before taking	0.03
After 15 grains	0.025
" 60 "	0.06

Roselle. The ammonium chloride was taken in 5-grain doses every two hours.

Before taking	0.02
After 15 grains	0.03
" 60 "	0.095

There was a marked contrast in the ammonia nitrogen reactions of the saliva and sputum. The reaction of the saliva was always faint even under full dosage of ammonium chloride and when the intensity of the reaction in the sputum was progressively increasing.

SUBJECTIVE OBSERVATIONS. Dr. Weems. Mild bronchitis of only several days' duration. Treatment begun on the second day of the attack with ½-grain doses of ammonium chloride at two-hour intervals. Distinct loosening of the sputum and diminished roughness of the tracheal and bronchial mucous membrane followed. The taste of ammonium chloride was evident in the sputum at first, later the sense of taste for all substances was blunted.

Self observations: Severe bronchitis of several weeks' duration. Treatment was begun at once, but was suspended from time to time and resumed for the purpose of repeating the experiment. The ammonium chloride was taken at first in ½-grain doses every two hours and later in doses of 5 grains at the same intervals.

Whenever the drug was stopped the sputum became less abundant, more tenacious, and more difficult to expel, and a sensation of dryness or tightness developed in the chest. When the drug was resumed the opposite effects were observed. The action of the drug

always developed within one-half to one hour. The experiment was repeated too often to permit of doubt as to the accuracy of the observations.

Another fact of special importance was noted. For twelve or thirteen hours after a dose of ½ grain (the drug having been taken at two-hour intervals during the previous twelve hours) the taste of ammonium chloride, which is unmistakable, was evident in the sputum as it passed through the mouth. This observation possesses double significance: it identifies the form in which ammonium chloride is excreted by the bronchi (which was not established by the chemical analysis) and it demonstrates that the excretion of ammonium chloride is relatively slow in man—that is, in ½-grain doses every two hours it is ingested more rapidly than it is eliminated by all channels through which it leaves the body. The rate of excretion bears upon the question of the supposed transformation of ammonium chloride to urea by the liver which has been referred to.

Mode of Action. The mode of action which appears most plausible is that ammonium chloride, during or after its excretion, or both, lessens the viscosity of the mucus, partly through increasing the water of secretion and partly through solvent action, and that then the normal mechanisms of removal come more readily into play. Being less viscid the mucus is carried by ciliary action more rapidly toward the upper respiratory passages and finally is expelled from them by the act of coughing.

One of the experiments of Henderson and Taylor[6] may be interpreted as corroborating this view, though they cited it to disprove the expectorant action of ammonium chloride.

According to their protocol they exposed the mucous membrane of the trachea of a dog to view and measured the rate at which charcoal travelled through ciliary action. They found that human saliva could travel at the same rate, but that the actual rate depended upon the thickness of the layer. Weak solutions of ammonium chloride and ammonium carbonate, directly applied, did not increase the rate of the saliva beyond that of the charcoal. The addition of water increased the rate to a maximum as effectively as did the ammonium salts. They concluded that the viscosity of the saliva was of more importance than the salts in solution.

If it be assumed that ammonium chloride in its passage through the bronchial wall increases the water of secretion, the contention in favor of the expectorant action of the drug receives strong support from this experiment. According to this experiment, ammonium chloride does not increase ciliary motion. The experiment also removes the necessity of seeking an explanation for the expectorant action of the drug in stimulation of the bronchial gland centres or in stimulation of peristalsis in the bronchioles.

[6] Jour. Pharm. and Exp. Therap., 1910, xi, 153.

SUMMARY. Clinicians generally believe that ammonium chloride is an expectorant. This action has been denied, however, on the basis of experiments on laboratory animals in which important factors were not controlled.

The action of the drug has been reinvestigated on patients suffering from acute and chronic bronchitis. The objections which have been raised to such experiments are not fundamental.

The excretion of ammonium chloride as such in the bronchial secretions has been proved.

Subjective observations have shown that ammonium chloride facilitates expectoration.

On the ground of these facts it is claimed that ammonium chloride is an expectorant within the definition of the term. It probably acts by increasing the water of secretion and softening the mucus.

A STUDY OF PROXIMO- AND ACRO-ATAXIA IN TABES DORSALIS.[1]

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(From the Department of Neurology of the University of Pennsylvania.)

THIS study of ataxia in early cases of tabes was undertaken because of a recent paper published by an excellent observer,[2] in which it was stated definitely that in tabes dorsalis, ataxia of the proximal extremity of the limb occurred earlier and could be demonstrated before acro-ataxia or ataxia of the distal portion of the limb.

This hypothesis was used as a means of differentiating between tabes and the subacute combined degeneration of the cord occurring in pernicious anemia, it being asserted that in early tabes there was demonstrable ataxia of the proximal extremity of the limb, before acro-ataxia or ataxia of the distal portion of the limb occurred, differentiating it from the ataxia occurring in subacute combined degeneration of pernicious anemia which appears in the reverse order.

Such a statement, if correct, coming as it does at a time when the sequence of the development of symptoms occurring in pernicious anemia with cord changes is receiving a great deal of study, would afford valuable assistance in making a differential diagnosis.

[1] Read by invitation before the Philadelphia Neurological Society, April 28, 1916.

[2] Hoover, C. F., The Significance of Acro-ataxia and Proximo-ataxia, AM. JOUR. MED. SC., 1915, cl, 651.

However, it does not quite fit in with the symptoms one would expect from the histopathological changes in the cord in the two conditions.

For the purpose of study of the ataxia in tabes, only very early cases were selected from those applying for treatment at the dispensary of the University of Pennsylvania in the service of Dr. William G. Spiller.

At the end of six months only ten cases were selected for this study, which were, with but one exception, in the pre-ataxic stage. I wish to emphasize that all cases studied represented early tabes, and by consulting the accompanying chart it is seen that cases with marked or even moderate incoördination in the performance of the usual tests for ataxia were not included. The chart also shows the symptoms upon which a diagnosis was made. It will be noted in the chart that all but three of these patients have been able to perform their usual avocation. The three exceptions quit work chiefly because of pain.

It may not be amiss to review hastily the present conception of the factors which enter into ataxia, or, better still, the incoordination of tabes.

Jandrässik,[3] in 1880, formulated the cerebral theory of ataxia. He believed that the centers for coördination and association in the brain were alone responsible for this symptom.

Raymond[4] enlarged this theory, especially as regards the psychological side, chiefly because the favorable results obtained by him in reëducation were attributed to the cerebral origin of the condition.

Frankel[5] in his monograph discusses the various theories, and arrives at the conclusion that ataxia is the result of interference with the centripetal fibers before they reach the brain.

Dejerine in discussing locomotor ataxia says that "Ataxia is central in the sense that the full activity of the central coördinating mechanism is profoundly modified by the disturbance of excitation which comes to it normally from the periphery. It is then not absolutely just to say that it is a modification of sensation from the periphery due to solution of continuity of the pathway for sensory impression to coördinating centers."

Oppenheim assumes that the coördination of muscular function is regulated mainly by centripetal impulses which do not become conscious sensations, and describes ataxia in this sense as sensory.

Comparison of the Regional and Anatomical Distribution of the Lesions in the Spinal Cord in Tabes Dorsalis and in Pernicious Anemia. In the subacute combined degeneration of the cord in pernicious anemia the thoracic region shows the

[3] Frankel (quoting Jandrässik), Tabes Dorsalis, p. 19.
[4] Frankel (quoting Raymond), Tabes Dorsalis, p. 19.
[5] Tabes Dorsalis.

first pathological changes; therefore, we should expect a disturbance of the sense of position and passive movement of all joints below this point, and the disturbance would be as early of the proximal joints as it would be of the distal.

The simultaneous involvement of the lateral columns of the cord would seriously interfere with this determination, since such an involvement necessarily leads to a hypertonicity of the limbs. In all except one of the few cases of pernicious anemia with cord changes which I have examined I could not determine whether proximo-ataxia existed for this reason. The one exception was a very early case in which there was increased reflexes and in which I was able to determine disturbances of the sense of position and passive movement in the shoulders and elbow joints when no other joints were involved.

In tabes beginning as the lesion usually does in the lumbar region of the cord, one should expect to find that the proximal joints of the legs would first show disturbance of joint and muscle sense, but such has not proved to be the case in the patients subjected to more delicate tests than those ordinarily used clinically.

Considering the lesions as to character and extent within the cord, there is found in tabes a distribution of the degeneration in the posterior columns quite different from that found in anemia. Regardless of whether one accepts the view of Obersteiner and Redlich or of Nageotte as to the primary lesion in the posterior roots in tabes, the changes in the posterior columns are axonal degenerations with glial replacement distributed in the white substance as a wedge-shaped area, the apex of which is directed toward the median commissure of the cord, and the base parallel to the posterior roots, leaving the cord substance along the posterior septum in the lumbar region free until later in the course of the disease.

The distribution of the lesions is the determining factor in the early clinical symptoms. It accounts for the interference with the sensory component of the reflex arc, resulting in loss of reflexes and a disturbance of muscle tone.

The involvement of the posterior roots and their ganglia produces trophic disturbances in the regions supplied, which, combined with the destruction of the reflex arc results in a hypotonic condition of the limb.

Fibers to Clarke's column and the cells themselves are early and constantly involved in tabes, with the result that the unconscious impulses from joints, muscles, and tendons are seriously impaired.

Hypotonia and loss of unconscious afferent impulses from skeletal structures are earlier signs in tabes than the loss of position sense and recognition of passive movements, and are of greater importance in the production of ataxia.

The cord changes in pernicious anemia, due as they are to some so far unknown hemolytic agent, shows an entirely different patho-

logical character and anatomical distribution, which appears to be largely determined by the distribution of the blood supply. The lesion is a periaxonal degeneration beginning in the posterior column along the posterior median septum with involvement of the lateral columns. The pathological alteration consists primarily of a degeneration of the medullary sheaths and later destructive of the axis-cylinders with in some regions but little glial proliferation as evidenced by the reticular appearance of the section. The distribution of the lesion along the posterior septum leads to a definite clinical syndrome, which is: disturbance of afferent impulses from the skeletal structures; loss of vibratory sense; disturbance of stereognostic perception; inability to distinguish between two points of the compass.

From the anatomical location of the lesion in the two conditions and the greater intensity of the degeneration in the posterior columns earlier in pernicious anemia, with the resulting disturbance of function, we should expect that in pernicious anemia loss of the sense of position and passive movement must be earlier symptoms than in tabes, although static and dynamic ataxia are not demonstrable early symptoms. This naturally leads to the pertinent question as to why the degeneration in pernicious anemia, located in the cord in such position as to interfere seriously with the recognition of the impulses from the skeletal structure, does not produce early incoördination upon volitional movement. This, to my mind, is due to the fact that the lateral columns are also involved, producing a hypertonicity of the muscular apparatus, which is directly opposite to the hypotonicity in tabes. Therefore, one must consider hypotonicity as of great importance in the causation of the ataxia in tabes. An equally important factor is the loss of unconscious impulses of equilibrium which occurs early in tabes and relatively late in subacute combined degeneration of the cord in pernicious anemia.

Incoördination or ataxia is shown by the fact that upon volitional movements the object is not attained in the shortest way nor with the requisite amount of force, and insofar as it relates to the cord changes in tabes it is the result of an interference with centripetal pathways, which renders it distinct from asynergy of central origin. It is not alone a dynamic but static ataxia as well. Continual intervention with the sensory impressions which come from the objects around us as well as from moving parts of our bodies are important factors in the production of ataxia. There is no difference, insofar as ataxia is concerned, between the movements of a healthy person in the performance of some new complicated act, and the movement of a tabetic in the performance of an act familiar to him. Both are due to irregularity of muscular movement, the result of faulty knowledge of the proper inervation necessary for the performance of the act. Therefore, all movements to

determine ataxia should be those with which the individual is familiar.

In addition to the ordinary movements used to determine ataxia, such as the finger to nose, the finger to toe tests, buttoning of clothing, Romberg's sign, etc., I have devised a system of charts to determine degrees of ataxia not sufficient to be brought out by the usual clinical means. By these charts I have endeavored to eliminate the action of certain muscle groups except those used in the performance of the test. While this is possible for practical purposes they are open to some degree of criticism or purely theoretical grounds.

The following methods were used for the upper extremity:

For the full arm movement a large sheet of paper is used upon which a circle three feet in diameter is drawn. Within this, by means of a rubber stamp, twenty-four circles are made, each being one inch in diameter and at equal distance from each other, there being two rows around the margin of the circle.

In the performance of this test the chart is placed against the wall, the center of the circle being on a plane with the patient's eye. He is then instructed to mark a cross with a pencil in the circle, being careful to start and stop the pencil mark on the margin of each circle. To determine disturbance of flexion and extension of the elbow, lines are drawn across a sheet of paper, an effort being made to start and stop the pencil mark on given base lines. In making this test the patient was seated at a table with the elbows resting on its surface, and the lines were drawn by a movement of the elbow.

For determining the coördination of the wrist a sheet of paper was used upon which were placed small circles one-fourth of an inch in diameter arranged in such a way that the lateral movements of the wrist were used in reaching the circles, within which a cross was made. It is in this test impossible to rule out some slight movement of the finger joints.

To determine incoördination of finger movement a figure of five rectangles was made with a rubber stamp, each side of a rectangle being one inch in length, the object of the test being to determine any degree of incoördination of movement made in tracing the lines of the figure. In this test as well as in the preceding one the elbow is fixed. Methods used for the lower extremities:

For the full leg movement a sheet of paper was used upon which circles one inch in diameter were made. On different parts of the surface sufficiently far apart to bring out all movements of the fully extended leg. In performing this test the patient stood on one foot, one arm being on a fixed support, to insure steadiness of the trunk and one limb, leaving one limb free for the test. A leather device closely fitting the big toe, and containing a marker, was used to place the mark within the circle.

To determine incoördination of the lower limb, as shown by dismetria in drawing lines, the patient was seated, thereby eliminating, largely, movements of the hip joint and with the device previously mentioned directed to draw lines on a plain surface, as was done in determining dismetria of the elbow-joint.

For the purpose of determining coördination of flexion and extension of the ankle joint and great toe a series of circles one-fourth of an inch in diameter were arranged in an arc, the extreme figures being eight inches distant from each other. The patient being seated and the limbs to be tested resting easily at right angles with the body, he was instructed, using the pointing device on the toe, to place a mark in the center of each circle.

Needless to say that the patients were all carefully instructed and allowed to perform the movements before the test was made.

The accompanying table will show graphically the various disturbances presented in each case.

It is seen that the most marked variability exists as to the predominance and frequency of any one symptom, and that ataxia, as shown by the Romberg, finger to finger, finger to nose, and toe to finger, tests have been relatively normal in all cases.

As regards ataxia in the execution of the full arm movement, it is seen that there is, in five cases, some slight disturbance, and in the same individuals there is more marked disturbance in the distal joints of the limb. Also that marked ataxia of the distal extremity of the limb was present in nine instances.

It is true that the finer muscular adjustments necessary in the performance of a complex act would show ataxic disturbances earlier than a less complicated movement, but certainly simple tracings over the lines of a rectangle is no more complex for the fingers than marking in circles would be for the full arm.

A surprising feature was the ability with which the greater number were able to use the full movement of the extended leg in the performance of the test, but all of the cases except one showed a variable degree of ataxia in the movement of the ankle and great toe. This exception was a well-trained athlete whose muscular coördination was perfect, although the patellar reflexes were difficult of determination even with reinforcement, and the tendon Achilles reflex was lost.

One important point brought out in the determination of the ataxia was the uncertainty and hesitation before beginning of the movement and evident difficulty with which the limb was stopped after the performance of the test was complete. This is the most important single factor in determining the degree of ataxia and does not show in the charts.

Conclusions. From a study of the anatomical distribution of the lesions in the cord in the two conditions, it is fair to conclude

that ataxia, occurring in early tabes, is in a large measure the result of an interference with certain afferent fibers which results in hypotonia and from the loss of the afferent impulses concerned in equilibrium, with the subacute combined degeneration of the cord in

No.	Pupil.	Pain.	Sensory disturbance.	Disturbance over chest.	Bladder.	Blood Wassermann.	Romberg.	Gait.	Patellar reflexes.	Achilles reflexes.	At usual occupation.	Vibratory sense.
1 D 2 C	Argyl Robinson Left pupil Argyl Robertson	In legs Marked in legs	None None	Sense of constriction Girdle sensation	Yes Yes	Positive ++	No No	Slight ataxia Normal	Lost Diminished	Lost Active	No Yes	Normal Normal
3 C	Sluggish reaction to light	Variable in legs	Normal	Constriction of thorax	Yes	+	No	Normal	Diminished	Normal	Yes	Normal
4 H 5 P	Argyl Robertson Argyl Robertson	Pains in legs Pain, fifth nerve distribution	Around waist General	Constriction of thorax Moderate	Yes Normal	+++ Unknown	Slight Slight	Normal Difficulty at night	Decreased Lost	Lost Lost	No Yes	Marked disturbance over face and head Normal
6 C 7 A	Pupils irregular Unequal and sluggish pupils	Pains in knee Marked	Over chest Normal	Around chest Normal	Normal Slight	+ Negative	Slight Slight	Normal Normal	Normal Normal	Lost Lost	Yes Yes	Decreased over legs Normal
8 W	Left pupil Argyl Robertson	None	Normal	Normal	Normal	Negative	None	Normal	Markedly diminished	Lost	Yes	Decreased over legs
9 M 10 FP	Pupils normal Sluggish reaction to light	Marked in legs None	Normal Cushion sensation over feet	Normal None	Yes None	Negative Negative	Slight None	Disturbed at night Slight disturbance	Lost Active	Markedly diminished Absent	No Yes	Normal

pernicious anemia, it is due more exclusively to an interference with afferent fibers carrying impulses from the skeletal structures, *i. e.*, sense of position and passive movement and muscle sense. It may, I believe, also be assumed that the lesions in tabes by reason of their distribution, are of greater importance in the production

of ataxia than the lesions in pernicious anemia, and that hypertonicity tends to limit the degree of ataxia. From the clinical methods used, it is found that in tabes there is a more frequent and more marked ataxia in the distal than in the proximal articulations

Joint sense.	Finger to finger.	Finger to nose.	Toe to finger.	Buttoning clothing.	Full arm movement.	Elbow.	Wrist.	Fingers.	Full leg movement.	Ankle.	Ankle and toes.
Normal	Normal	Normal	Normal	Clumsy	Slight	Marked	Marked	Marked	Moderate	Marked	Marked.
Normal	Normal	Normal	Normal	Normal	Normal	Normal	Slight	Marked	Normal	Normal	Slight.
Normal	Normal	Normal	Normal	Normal	Slight	Normal	Slight	Moderate	Normal	Slight	Normal.
Normal	Normal	Normal	Normal	Slight clumsiness	Slight	None	Marked	Marked	Moderate	Marked	Marked.
Disturbance in hands and toes	Normal	Normal	Normal	Normal	Slight	Slight	Slight	Slight	Normal	Moderate	Slight.
Normal	Normal	Normal	Normal	Normal	Normal	Normal	Marked	Moderate	Normal	Normal	Marked.
Normal	Normal	Normal	Normal	Normal	Slight	Normal	Marked	Moderate	Normal	Slight	Moderate.
Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal.
Normal	Slight disturbance	Normal	Normal	Normal	Normal	Normal	Marked	Marked	Normal	Normal	Slight.
Lost in three outer toes	Slight disturbance	Slight	Normal	Slightly clumsy	Normal	Marked	Marked	Marked	Normal	Not tested	Not tested.

of the limb, and that the distribution of the ataxia cannot be used clinically as a means to differentiate tabes dorsalis from the subacute combined degeneration of the cord which occurs in some cases of pernicious anemia.

TUBERCULOSIS (CONCEALED): A HITHERTO UNRECOGNIZED CLINICAL TYPE.

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Tuberculosis, like its great companion disease syphilis, may present itself in a variety of clinical pictures, some of them easy of recognition and well established as clinical types, others more obscure and difficult to interpret, and still others as yet unrecognized.

One of the peculiarities of the tubercle bacillus, shared in by the spirochete of syphilis and the bacillus of leprosy, is the tendency which it often manifests to invade its host without at first causing much constitutional or local reaction and without producing pronounced symptoms indicative of its presence. This reaction on the part of the organism to the tubercle bacillus is often expressed only in terms of a mild toxemia and not the recognized clinical types which have been so often emphasized and so often described, and which the profession has too often considered as a *sine qua non* in order that a diagnosis of tuberculosis shall be made.

Tubercle bacilli often multiply very slowly in the human body and establish a firm foothold only after a long series of years. The symptoms expressing a rapid and violent reaction against the infection namely, fever, chills, loss in weight, pain, sweats, cough, etc.—so commonly encountered in the more pronounced clinical pictures, are wanting in these individuals. So widespread is this slow-burning concealed type of tuberculosis, and so varied is its symptomatology, that the clinician should always be upon the lookout for it and never consider that an obscure case, exhibiting symptoms of nervous and physical exhaustion, has been thoroughly studied until he has excluded it.

The various symptomatic pictures built around clinically recognizable tuberculous infections in the lungs, pleura, peritoneum, adrenals, meninges, joints, etc., the manifestations of which have been so carefully described by medical writers, do not concern us in this paper. Our attention is focused upon a hitherto unrecognized class of tuberculous individuals exhibiting toxic symptoms without localizing focal evidence of the disease, persons as certainly infected as those of the recognized type. Mendelsohn in 826 deaths from accident and violence found 20 per cent. of the individuals with healed or active tuberculous lesions. Concealed tuberculosis is therefore a common pathological state. Do such persons have complaints or abnormal sensations not experienced by the normal individual? If so, what are they? Is the presence of the tubercle bacillus responsible for these symptoms, or do these persons go about in a state of apparent health unconscious of the smoldering fires

burning within? These are pertinent questions for consideration, and yet almost no attention has been paid to the symptoms of persons harboring this form of the disease, and no one, so far as I know, has attempted to work out a symptom syndrome which will assist in identifying it.

I wish to emphasize this fact. The profession has trained itself to consider only those sick persons as having tuberculosis in whom there can be found objective focal evidence of the disease in some organ of the body, the lungs, peritoneum, pleura, kidneys, or elsewhere. If this evidence is wanting, even though the individual may show well-marked signs of an abnormal physical and nervous state, we have not been ready to admit that tuberculosis exists, and even if we do admit its existence, we have not been willing to consider the presence of the tubercle bacillus in the organism as an etiological factor in the production of the symptoms of which the patient complains. That is, the clinical picture presented by tuberculosis (concealed) in the silent areas of the body, mediastinal or postperitoneal lymph glands, lungs, pleura, peritoneum, pericardium, and elsewhere, where no local objective signs can be detected to indicate its presence, and where the individual shows only the evidence of the slow-burning fires of a tuberculin toxemia without the presence of symptoms and clinical signs expressive of the localizing ravages of the bacillus itself, is not recognized as a clinical entity.

The symptoms of nervous and physical exhaustion associated with recognizable tuberculosis have been long recognized and dwelt upon by all writers upon this subject; but that persons showing symptoms of nervous and physical exhaustion (toxic symptoms) and exhibiting no clinical evidence of tuberculosis could still be tuberculous, and that the quiescent, silent process could serve as the etiological factor, for the symptoms of physical and nervous exhaustion of which they complain has been overlooked. The profession has, therefore, gone on complacently stamping its brand of neurasthenia, asthenia, nervous exhaustion, psychasthenia, Glénard's disease, etc., upon those poor creatures, adults and children, in whom no organic cause could be detected to account for the symptoms of which they complain without attempting to determine whether a form of tuberculosis exists which exhibits no physical signs and which can only be detected by a specific (tuberculin) test.

The clinical conception of this type of tuberculosis I can best illustrate by the history of a case of lues which came under my observation some years ago.

The patient was a married woman, aged forty-five years, without children. She was well and strong up until her twenty-fifth year, when she began to develop a peculiar train of symptoms, interpreted by various physicians in this country and abroad as nervous exhaustion. She lost weight, became somewhat anemic, tired easily, had spells of faintness, and most peculiar attacks in which while

walking upon the street or sitting conversing with friends or at the theatre she would suddenly feel as if a great dark cloud were descending over her, objects were seen and heard at a distance as though looked at through smoked glass. She would become dizzy, and if standing must sit down. After a few moments the attack would pass off. If she were walking upon the street and the attack came on she would support herself by leaning against a building or some near object. Years went by without relief. She became weak and prostrated; all mental and physical exertion tired her; her memory became poor; she expressed herself as good for nothing; living a vegetative existence; going about as in a dream; interested in no one. She lost weight, became depressed, and disheartened. One consultant after another examined her only to state that he could find nothing organic, and that she was suffering from nervous exhaustion.

A careful physical examination of this patient was negative for organic disease. Not a single recognizable symptom or sign of syphilis could be detected. She had a slight secondary anemia. The Wassermann reaction, which had not before been taken, was strongly positive. With this information the patient was questioned closely, and finally recalled that when a young woman, and while engaged to be married, a sore appeared upon her lip similar to one which had for sometime been upon the under lip of her fiancé. She had consulted a physician, who had given her medicine for her blood, and the sore had finally healed. She had never had other symptoms or signs of a luetic infection. Her physician had never told her the nature of the infection.

A diagnosis of syphilis was made. The patient was immediately placed upon specific treatment. The result of a year's treatment was marvelous. From a weak, nervous creature of no use to herself or anyone else she became a strong, energetic, active woman, the attacks of exhaustion, with dizziness and faintness, gone, memory restored, weight regained, able to fulfill her function in life, and interested in the affairs of her home and society.

Now here was a patient with lues, suffering from the infection, but without a single recognized symptom or physical sign suggestive of the disease in any organ or tissue of the body. Because of the lack of these symptoms and signs the various diagnoses of neurasthenia, psychasthenia, and nervous exhaustion had been made. It was syphilis without the focal signs of the disease. It was syphilis revealed by a specific test and not by clinical symptoms or physical signs. The patient was, however, as truly suffering from the disease as if she had had gummata in her liver or necrotic bone lesions.

Now it is in exactly this sense that we must view the clinical picture here proposed, expressing a symptom type of tuberculosis so hidden that it many times cannot be detected by any means except a specific test; persons complaining of symptoms of nervous

and physical exhaustion over years, in whom an exhaustive examination failed to disclose the presence of tuberculosis, just as in the case of lues cited the examination failed to detect the signs of syphilis, and in whom the presence of a tuberculous infection was determined just as the presence of syphilis was determined in the case cited above by the use of a specific test.

The following case is an example of this form of tuberculous infection to which I refer:

Miss E. L., aged twenty-three years, single, living at home, admitted to St. Barnabas's Hospital October 14, 1913, complaining of backache, insomina, spells of depression, and attacks of indigestion. Her family history was negative. When a young girl she had a playmate who later developed and died of tuberculosis of the lungs. The patient herself has never been very strong even as a child. Her past history included a long series of illnesses of various sorts: curvature of the spine at five years of age, at first thought to be tuberculous, later considered hysterical; chorea at ten years of age; dysmenorrhea at fifteen years associated with fainting spells and exhaustion, often keeping her in bed for days at a time during her menstrual period; various abdominal operations performed at different times, terminating in hysterectomy in February, 1912; no cause given by the operating surgeon for the hysterectomy other than that it was considered best for the patient's general state of health. No pathological lesions found at operation.

The history of the patient's present complaints dates back over a number of years and includes a long series of symptoms of indigestion, abdominal pain, backache, insomnia, constipation, fermentative indigestion, attacks of mental depression, crying spells, dizziness, aching in the neck, headache, and eye ache. Patient stated that she never had a good appetite, that the daily routine of her life exhausted her, and year after year found her building up from one attack of exhaustion only to relapse into another. She had lived a semi-invalid existence. She had tried to work at various times, but always had to give up because she became so tired and exhausted. She had had a slight nervous cough at times, but had never coughed sputum. Many consultants had examined her lungs, but had found nothing. In the last year the patient had lost about fifteen pounds in weight. In order to improve her digestion, she had dieted to such an extent that she could scarcely eat solid food of any kind.

Patient was a tall, angular-looking girl. High cheek bones, long chest and abdomen. Throat and teeth negative. Marked tremor of the upper eyelids with the eyes closed. Increased knee-jerks. Pupils reacted to light and accommodation. No incoördination. Some tremor of the finger tips. No enlargement of the thyroid; no exophthalmos. She presented all the stigmata of a highly nervous girl. Hands, arms, and legs twitched during the examination. She seemed melancholy and depressed.

A careful physical examination of the patient, including a searching examination of the lungs, revealed no evidence of organic disease. There was a moderate gastroptosis, dislocated kidney on the right side, some tenderness over the abdominal aorta and along the lower spine. Urine and gastric examinations were negative. No occult blood in stools. Blood was negative except a slight secondary anemia; hemoglobin, 87 per cent. Wassermann reaction negative. Von Pirquet test positive.

Patient was studied in the hospital over a period of two weeks. She had occasional rises in temperature to 99.2°; pulse 85 to 100. No definite diagnosis could be made. She presented all the earmarks of a highly neurotic young woman suffering from nervous and physical exhaustion. She had frequent crying spells, much mental depression. She had occasional attacks of indigestion, was bothered much with insomnia, complained of cold hands and feet, backache, headache, and had a slight clearing of her throat. There was no sputum. On two different occasions she had fainting spells while going to the bathroom. Roentgen ray examinations of the spinal column and lungs negative.

The prolonged series of ailments and complaints dating back to girlhood, the symptoms of physical and nervous exhaustion, the absence of evidence of organic disease, seemed to justify the diagnosis of neurasthenia. But what kind of a diagnosis was neurasthenia? Why exclude syphilis in this case by a negative Wassermann reaction and fail to exclude tuberculosis by a tuberculin test?

On the fifteenth day after admission patient was given $\frac{1}{20}$ c.c. of a Bureau[1] tuberculin (5 mgms. of Koch's Old Tuberculin) and within sixteen hours exhibited a positive reaction, temperature going to 102°. Following the positive tuberculin test the clinical diagnosis of neurasthenia was abandoned and the diagnosis made of tuberculosis (concealed), focus not determined, with chronic tuberculous toxemia exhibiting symptoms of physical and nervous exhaustion.

Now here was a patient with tuberculosis but without a single recognized physical sign of the disease in any organ or tissue of the body. It was tuberculosis without the focal signs of the disease. It was tuberculosis without the well-known recognized symptoms of the disease. It was tuberculosis revealed by a specific test and not by clinical symptoms and physical signs. This patient was, however, as truly infected with the tubercle bacillus as if she had had a consolidated area in the apex of the right lung or tuberculous lymph glands of the neck. In the one case the location of the bacillus is known, in the other it is not known. Surely the failure to locate the lesion is no good reason for denying the diagnosis provided it rests upon good grounds.

[1] This tuberculin is a 10 per cent. solution of Koch's Old Tuberculin, and is made by the Bureau of Animal Industry at Washington.

While it must be admitted that this individual is tuberculous and is negative for other organic disease, the evidence presented does not establish a casual relationship between the symptoms of physical and nervous exhaustion and the tuberculous process. "Is not the case presented really a patient with neurasthenia harboring an associated tuberculous process?" Such an interpretation of this case is unreasonable. If some one will demonstrate a pathological base for neurasthenia, so that it can be identified and differentiated from other diseases of known pathology the discussion upon this phase of the subject might be properly continued. In the absence of such lesions and with reliable proof of the existence in this person of a tuberculous process, and that only, it is only reasonable to conclude that the symptoms of which the patient complains is an expression of a disease (tuberculosis) which is common and about which we know a great deal, and which in its recognized forms often expresses in the highest degree symptoms of nervous and physical exhaustion, rather than a name, a symptom-complex, about which we know nothing.

But the question may be raised, "What pathological evidence can be offered to prove that a tuberculous lesion exists in this individual?" Pathological proof in this instance is impossible. Patients like this one are living. When they do die and are examined of what value is the evidence? If a tuberculous lesion were present at autopsy how could one know that it was there at the time the patient complained of her symptoms? If a tuberculous lesion were present and healed, how could one know that it was healed at the time of the patient's illness? If it were present and active, how could one know whether the lesion had been present and active at the time the patient complained of her nervous and physical exhaustion? Postmortem and clinical experience has proved the reliability and specificity of a positive subcutaneous test as proof of the existence of an active tuberculosis. Further evidence than this need not be carried into court in settling the question raised.

The diagnosis in this case, just as in the case of lues previously cited, rests upon a specific test. This in itself is the best evidence which can be offered to prove that the patient is harboring a tuberculous process.

In a previous paper[2] I presented a careful study of fifteen cases such as has been here described, all negative for other organic disease and all proved to be tuberculosis by an injection of tuberculin, and pictured this symptom type of quiescent or what I preferred to call "concealed tuberculosis" as follows:

"A person usually under twenty-five years of age, with, or sometimes without, a history of known exposure to tuberculosis, often dating back to childhood, comes complaining of a varied lot of symptoms expressing nervous and physical exhaustion, the most

[2] Jour. Am. Med. Assn., 1914, lxiii, 996.

common of which are indigestion, headache, constipation, mental depression, cold hands and feet, backache, neckache, eyeache, voice tire, clearing of the throat, crying spells, chilliness, and loss of weight. These symptoms have dated back over a number of years with period of improvement followed by relapse under unusual nervous or physical strain. Partial or complete breakdown often results.

On inspection one notes a poorly nourished, high-strung person with angular features, high cheek bones, long chest and abdomen, slender arms and legs, and active reflexes.

A careful physical examination reveals no positive evidence of organic disease. Enteroptosis is usually present. Normal or doubtful lung signs are usually encountered. The pulse-rate is, as a rule, increased, the temperature record may be normal or show an occasional afternoon rise to from 99.2° to 99.4° or more. The laboratory findings, including Wassermann test, are negative for organic disease. The roentgen-ray studies of the lungs for tuberculosis show positive, doubtful, or negative signs.

The long history of physical and nervous exhaustion with many relapses, the build and nervous construction of the individual, the absence of the signs of organic disease lead to the diagnosis of neurasthenia (so-called). The patient, however, usually gives a prompt von Pirquet test and always reacts positive to a subcutaneous injection of tuberculin."

This is a clinical type of tuberculosis which should be recognized. It is a clinical picture of tuberculous toxemia without the focal evidence of the disease. It is tuberculosis revealed by a specific test.

Persons with this symptom-complex are negative for organic lesions other than those produced by the tubercle bacillus. With such information before him, what intelligent physician would still cling to a diagnosis of so-called neurasthenia?

Most persons exhibiting symptoms of physical and nervous exhaustion harbor disease of one kind or another provided the examination has been thorough enough to disclose it. Whether the disease is of tuberculous, syphilitic, cardiac, nephritic, gastric, thyroiditic, hemic, or septic origin must be determined in each individual case. Some so-called neurasthenics in whom a most careful examination fails to detect organic disease other than tuberculosis do not react to a maximum dose of tuberculin given subcutaneously. The percentage of such cases is, however, small if the examination is thorough and a large series is studied. I am contending for the recognition by the profession of a symptom type of tuberculosis which is an expression of the silent concealed form of the infection, the symptom-complex of which corresponds with the at present accepted symptomatic clinical pictures built around so-called neurasthenia.

These cases are common. They can be recognized by a specific (tuberculin) test. They should be diagnosed and treated as tuberculosis and not as some form of nervous exhaustion.

ACUTE HEART BLOCK OCCURRING AS THE FIRST SIGN OF RHEUMATIC FEVER.

By Paul D. White, M.D.,
BOSTON.

(From the Medical Service of the Massachusetts General Hospital.)

Acute heart block occurring in patients during the course of rheumatic fever has been reported by several writers, most recently by Christen Lundsgaard,[1] of Copenhagen, who mentions also other recorded cases, but the detection of an acute heart block prior to the finding of other signs of rheumatic fever infection is so unique and important as to deserve special mention. A patient has recently come under my observation who exhibited this condition. Of additional interest in this patient were the transient character of the block and the absence of any evidence of valve damage. In the case of transient heart block in rheumatic infection described by Lundsgaard,[2] in the case reported by Magnus-Alsleben,[3] in that of Cowan, M'Leod and Patterson,[4] and in three described by Mackenzie,[5] his cases Nos. 85, 87, and 88, there was no evidence of valve damage during the illness of the patient. In the patient described by Cowan, M'Leod and Patterson, a short soft systolic murmur was heard at the apex two months after the illness.

Case Report. A. J. B., aged eighteen years. Family and past history unimportant. Visited the out-patient department of the Massachusetts General Hospital December 16, 1915, because he ached "all over." Four days previously he had "caught cold," and since then he had had coryza, cough, headache, and backache. For a couple of days he had been bothered by palpitation, and for one day he had noticed lameness in his right arm, but he complained of no definite joint pain. No medicine had been taken.

Physical Examination. The boy appeared sick, but examination revealed nothing but redness of the throat (tonsils not large or inflamed), pronounced reduplication of the cardiac second sound heard best at the apex, and an irregularity of the pulse. The temperature was normal and the urine normal. The joints appeared normal. The seriousness of the lad's condition was not appreciated until the graphic record of the pulse was obtained.

A polygram of radial and jugular pulses (Fig. 1) showed very defective auriculoventricular conduction with marked prolongation of the *a–c* interval (up to 0.5 second), frequently leading up to dropped beats. In the venous tracing the *a* and *v* waves occur

[1] Lancet, London, 1916, exc, 125.
[2] Loc. cit.
[3] Ztschr. f. klin. Med., 1910, lxix, 82.
[4] Quart. Jour. Med., 1910, iii, 115.
[5] Diseases of the Heart, London, 1913, 456.

together, producing the very high excursions. Right or left vagal pressure increased readily the degree of block.

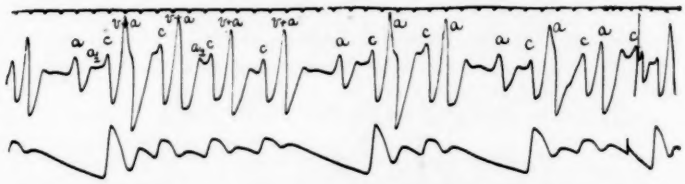

FIG. 1.—Polygram taken December 16, 1915, showing heart block with very long a–c interval (up to 0.5 second) and occasional dropped beats. Upper record is of jugular pulse, lower of radial pulse. Time interval = 0.2 second. This and subsequent tracings reduced to about $\frac{2}{3}$ original size.

After establishment of this diagnosis of heart block, apparently of infectious origin, the patient went to bed, where he remained for the next two weeks, suffering from a severe attack of acute polyarticular rheumatism. The joint symptoms began a few hours

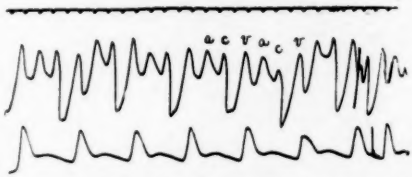

FIG. 2.—Polygram taken December 20, 1915, showing long a–c interval (0.3 second) but no dropped beats. Time interval = 0.2 second.

after the visit to the hospital, and in four days (December 20, 1915) the knees, toes, and right hand had all become involved with swelling, redness, pain, and tenderness. Treatment consisted of the administration of salicylates by mouth and of oil of gaultheria

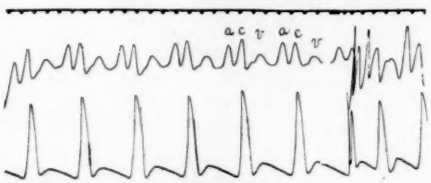

FIG. 3.—Polygram taken February 19, 1916, showing normal a–c interval (0.18 ± second). Time interval = 0.2 second.

applied to the affected joints. On December 20 a polygram (Fig. 2) showed no longer any dropped beats, but still a definite prolongation of the a–c interval.

On January 11, 1916, the patient again visited the out-patient department of the hospital and an electrocardiogram showed normal rhythm with a P–R interval slightly long (0.20 second). At this time he felt well except for slight pain in the left heel. No enlargement of the heart was made out and there were no murmurs. The reduplication of the second sound had disappeared. The joints appeared normal.

On January 29, forty-five days after the block was first discovered, an electrocardiogram showed normal rhythm with a perfectly normal P–R interval (0.145 second). At this time he felt well. On February 19, three weeks later, a polygram (Fig. 3) showed a normal *a–c* interval (0.18 second) and the patient felt well except for rare short sharp pains in his precordia during work which he had resumed. The work consisted of heavy lifting and lighter work was advised. Physical examination at this time showed the apex impulse 2 cm. inside the nipple line in the fifth and sixth intercostal spaces. There was no systolic retraction at the apex. No murmurs or reduplication were heard; the first sound was soft. P2>A2 but not accentuated. Pulse rate = 72.

SUMMARY. A case is recorded in which acute and transient heart block appeared as the first sign of an acute rheumatic fever. The conduction time between auricle and ventricle showed great delay before the onset of the joint symptoms and returned to normal about six weeks after the block was discovered. In this case the myocardium not only gave the first evidence of the importance of the illness but also showed at least temporary damage while no evidence was found of endocardial or pericardial involvement.

The value of the graphic study of the pulse is well illustrated by this case.

REVIEWS

BLOOD-PRESSURE: ITS CLINICAL APPLICATIONS. By GEORGE W. NORRIS, A.B., M.D., Assistant Professor of Medicine in the University of Pennsylvania; Assistant Visiting Physician, University Hospital. Second edition. Pp. 424; 133 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

THE rapid exhaustion of the edition of a book does not necessarily show the inherent value of the book, as other factors, aside from the real worth of the work, may at times induce a ready sale. But this generalization does not apply to Dr. Norris's work which is now appearing in the second edition in a comparatively short time after the publication of the first. In this case it can be fairly stated that the first volume on blood-pressure was so complete and thorough, and so painstakingly prepared, that its wide-spread popularity was well merited. In this new edition Dr. Norris has incorporated much fresh material in the ever-changing and advancing study of vascular pressure. He has incorporated new researches, both clinical and laboratory, and in every way has kept abreast of his subject. There is one criticism, however, of the book which may be expressed. Dr. Norris is an authority on his subject, therefore it would enhance the value of his work were he to express more didactically his own opinions of the various methods and procedures which he discusses. In this way the less expert reader would have the definite opinion of one qualified to express, for example, which method is best in estimating the functional efficiency of the circulation. As it is now the book describes so many different methods that it is difficult to pick out the best one without guidance.

J. H. M., JR.

RULES FOR RECOVERY FROM PULMONARY TUBERCULOSIS. A LAYMAN'S HAND-BOOK OF TREATMENT. By LAWRASON BROWN, M.D., of Saranac Lake, New York. Second edition. Pp. 184. Philadelphia and New York: Lea & Febiger, 1916.

ANOTHER edition of Dr. Brown's excellent little book of *Rules* is heartily welcome. Though seemingly a simple task, it required an expert to present the subject so briefly, so entertainingly, and so

accurately. While such a book is in no sense intended as a substitute for the physician's instructions, it will in many instances be a valuable supplement to them. Besides directly applicable instruction, the book also contains much general information of a useful character about tuberculosis. It is to be hoped, however, that not only patients and other lay persons will profit by this volume, but that its valuable instructions will also be shared by physicians, medical students, and nurses. C. M. M.

DISEASES OF THE EYE: A HANDBOOK OF OPHTHALMIC PRACTICE FOR STUDENTS AND PRACTITIONERS. BY GEORGE E. DE SCHWEINITZ, M.D., LL.D. (Univ. of Pa.), Professor of Ophthalmology in the University of Pennsylvania; Ophthalmic Surgeon to the University Hospital; Consulting Ophthalmic Surgeon to Philadelphia Polyclinic Hospital, Philadelphia General Hospital, and Orthopedic Hospital and Infirmary for Nervous Diseases. Eighth edition. Pp. 754; 386 illustration and 7 colored plates. Philadelphia and London: W. B. Saunders Company, 1916.

WHEN a book passes through eight editions and a number of reprints in less than twenty-five years, on an average about one revision or reprint every second year, there is the best *prima facia* evidence that the work is one of real merit; and this is completely borne out by a perusal of the contents, however critical the reader may be. There is no exaggeration at all in declaring Dr. de Schweinitz's text-book to be the best of its kind in the English language, and unsurpassed in any other language. This is no slight praise, considering the high character of a number of books dealing with the same subject by other distinguished writers.

The subject-matter has been brought thoroughly up to date, although no epoch-making discoveries or improvements are to be chronicled in this domain since the last edition. We note that Lieutenant Colonel Elliot has written the description of the operation for glaucoma known by his name. The author observes of this method that he "is unconvinced that it is a better procedure than a technically correct iridectomy," while he regards it as a better operation in chronic non-congestive glaucoma than iridectomy and preferable to a second iridectomy or sclerotomy if a previous iridectomy has failed. He likewise is not very favorably impressed by Heine's operation of cyclodialysis as a substitute for iridectomy in ordinary acute or chronic glaucoma.

The typography, illustrations, paper, and general make-up of the volume are excellent and worthily represent the publishers' important contribution to a work of such merit. A full index completes the volume. T. B. S.

A Mechanistic View of War and Peace. By George W. Crile, M.D., Professor of Surgery, Western Reserve University. Pp. 104; 32 illustrations. New York: The Macmillan Company.

This small book will appeal to those who are familiar with Dr. Crile's other works and are in accord with his well-known theories. Although the book is in a sense descriptive of the present European war, yet it should not be read from this point of view but only as an interpretation of the phenomena of war upon the basis of the mechanistic theory. It is written from the view-point of this theory, in the terms peculiar to the theory, and upon one's belief in this theory, the value of the book will depend.

The quotation may help to make this clear. It is from the chapter entitled A Mechanistic View of German Kultur, p. 75: "A people may be brutalized into formal submission; but brutal treatment results in creating in the brains of the children the strongest action patterns of opposition and of hatred. The conquering enemy can never supplant the influence of the hating mother who plants action patterns in the brains of her children when the shades are drawn." O. H. P. P.

Medical Clinics of Chicago. Vol. 1, Nos. 5 and 6. Philadelphia and London: W. B. Saunders Company, 1916.

The fifth number of the *Medical Clinics* contains some very interesting and instructive case studies. Dr. Case contributes an article on roentgenological aspect of intestinal stasis. Dr. Williamson presents five different cases, of which the last one, showing the difficulty of distinguishing between carcinoma of the stomach and pernicious anemia, is most ably discussed. Dr. Preble has two cases which are interesting but marred by frequent questions and answers. Dr. Hamill discusses three neurological disorders. In Dr. Tice's clinics, in addition to the two cases that he shows, there is also a report on the autopsy of the case which was discussed in the January *Clinics*. Probably the most valuable and thorough of the different clinics is that of Dr. Abt, who has a splendid discussion on congential syphilis, which is illustrated by photographs and a colored plate. This number of the *Clinics* is concluded by the three cases of Dr. Mix.

The sixth number of the *Medical Clinics* contains, in addition to the authors in the previous number, also clinics of Dr. Hamburger, Dr. Tivnen, Dr. Friedman, and Dr. Zeisler. This number is uniformly good and contains some very interesting and valuable material. The clinics are all good, but it would be perfectly fair again to say that that of Dr. Abt is extremely carefully prepared

and well illustrated. Dr. Hamburger also contributes a clinic which elaborates most carefully the present-day treatment of diabetes as advocated by Dr. Allen.

This last number of the *Medical Clinics of Chicago* shows a very distinct improvement over the earlier ones. There are still some things to which one takes exception, but, on the whole, they are a most novel and interesting method of learning at first hand the ideas and methods of men competent to discuss and to teach internal medicine. J. H. M., Jr.

The Starvation Treatment of Diabetes. By Lewis Webb Hill, M.D., Children's Hospital, Boston, and Rena S. Eckman, Dietitian, Massachusetts General Hospital, Boston. With an introduction by Richard C. Cabot, M.D. Second edition. Pp. 131. Boston: W. M. Leonard, 1916.

This small book on the details of the Allen treatment may be reviewed both accurately and comprehensively by quoting the last paragraph of the introduction written by Dr. Richard Cabot. "It is, of course, too early to say how far-reaching and how permanent the effects of such a diet will be in the severe and in the milder cases of diabetes. All we can say is that thus far it appears to work admirably well. To all who wish to give their patients the benefit of this treatment I can heartily recommend this book."

J. H. M., Jr.

Character and Temperament. By Joseph Jastrow, M.D. Pp. 596. New York and London: Appleton & Co.

This volume is the first of a series on general psychological subjects, the others being entitled, "The Qualities of Men," "The Subconscious," and "Fact and Fable in Psychology." One or two have been previously reviewed in this Journal. In all of these volumes, and especially in this, the effort is made to clearly present the subject of the psychological elements of the mind. The reviewer is not at all certain whether these volumes are meant for the student of psychology or if it is an effort to popularize the subject. It is difficult to adequately review a book of this kind because the subject is so large and the presentation so difficult. The reviewer who has taught medical students for many years would hardly recommend this book to students because the method of presentation is not attractive. The paragraphs are large, many of them an entire page, and some two, and while one may conceive that a student of psychology would be sufficiently interested to read paragraphs of this sort, yet is this the wisest way to present any subject? T. H. W.

A Text-book of Histology. By Rudolf Krause, Professor of Anatomy at the University of Berlin. Pp. 274; 36 illustrations. New York: Rebman Company.

This appears to be intended as a companion book to Professor Krause's *A Course in Normal Histology*, published in 1913 and reviewed in Am. Jour. Med. Sc., May, 1914. This latter work was principally of the nature of an atlas of colored plates, with a descriptive account of each illustrated tissue or organ. The present work is a comprehensive text-book, illustrated for the most part with schematic explanatory figures. It is stated on the title-page that the references to illustrations given in the text relate to the colored illustrations in the previous larger work. Thus for a complete survey of the field of normal histology it would be necessary to have both books, as they are, in many ways, complementary to one another. One also learns from the title-page that this text was translated from an original manuscript and is now printed the first time. Considering this method of preparation the book is well done and only small errors of fact have been detected. But in the literal translation of some of the original names the writer has not always brought his terms into line with current nomenclature. This method of preparation has also its merits, for, no doubt, one gets a more vivid and interesting account of the subject when taken directly from the lecturer. Many more details of physiological chemistry are contained than usually given in current histologies, and, in many ways, the book represents an interesting exposition of the subject. W. H. F. A.

The New Public Health. By H. W. Hill, Professor of Public Health, Western University. Pp. 205. New York: The Macmillan Company, 1916.

In the several chapters of this book the author clearly brings out his contention that the old public health was concerned with the environment; the new is concerned with the individual. The vastness of the problem of prevention of disease is thus made comparatively simple. For example, if instead of improving the environment of the 100,000,000 people in the United States we give proper supervision to the 200,000 people infected with tuberculosis the problem is but one five-hundredth the magnitude.

Very strong emphasis is made of the care of infective discharges. Indeed this seems probably the most important factor in the new public health. Thus we see that tuberculosis, pneumonia, and the other infectious diseases will develop under almost any circumstances if the dose of infection be large enough, virulent enough, or

sufficiently repeated. These same diseases will not develop under any circumstances without such infection.

It is the belief of the author that mothers, because of intimate contact, propagate and keep alive and spread the infectious diseases of children more than any other one body of people. The basic principles of public health, therefore, should be taught in public schools in order to reach girls, the prospective mothers of the race.

The common fallacies and superstitions of a former generation, many of which are still believed in spite of their absurdity, are discussed in an interesting manner. The as yet unsolved problem of venereal prophylaxis is but lightly touched in this book.

The chapters are logically arranged, and each contains at the end a well-written summary. A. G. M.

AN INDEX OF TREATMENT. BY VARIOUS WRITERS. Edited by ROBERT HUTCHISON, M.D., F.R.C.P., Physician to the London Hospital, and Physician (with Charge of Out-Patients) to the Hospital for Sick Children, and JAMES SHERREN, F.R.C.S., Surgeon to the London Hospital and Senior Surgeon to the Poplar Hospital for Accidents. Revised to conform with American usage by WARREN COLEMAN, M.D., Professor of Clinical Medicine and Practical Pharmacology, Cornell University Medical College. Seventh edition. Pp., 1152; 82 illustrations. New York: William Wood & Co.

THE purpose of this work is to furnish the general practitioner with a complete and trustworthy guide to modern methods of treatment, in a convenient form for reference.

The list of contributors consists of eighty-nine British authors, many of whom are of such prominence as to assure the success of any work undertaken by them; and this, coupled with the fact that it has run through seven editions, gives it a warm recommendation.

The authors have avoided any unnecessary presentation of a confusing number of procedures and have adhered throughout to the most effective and direct methods. There are no chapters, the book starting with the treatment of diseases in alphabetical order, this order being maintained throughout. The surgical articles are devoted more to non-operative treatment and to minor or emergency operations of the type the general practitioner might be called upon to perform, while the technic of the more elaborate operations is omitted as is the management of labor, the latter being conceded to be without the scope of this work.

The description of treatment is very similar to that found in text-books of medicine, surgery, and the various specialties, and includes procedures for practically every diseased condition regard-

less of the field into which it falls. The descriptions of necessity fall short of the completeness of a system on treatment, in places being rather sketchy, while in others, as the blood diseases and rheumatoid arthritis, they leave nothing to be desired. The book is of unquestionable value to the general practitioner, who may encounter any of the conditions mentioned and who may not be fortunate enough to possess the various systems or the text-books of the specialties, which he as a practitioner may encounter.

The book is rather cumbersome in size, and the print is decidedly too small. Two volumes and larger print would be an advantage.

A. H. H.

TEXT-BOOK OF NERVOUS DISEASES. By CHARLES L. DANA, M.D. Eighth edition. Pp. 632; 262 illustrations. New York: William Wood & Co.

THIS is the eighth edition of this well-known work, the first being published twenty-three years ago. Comparing this with the previous edition there is the greatest difference, and it seems almost as if one is reading an entirely new work. There is little consideration given to anatomy, the author taking the position that in modern neurology any extensive discussion of anatomy is out of place, as special books are numerous on this subject. There is the usual treatment of symptoms, not much of a discussion on pathology and then the usual consideration of various clinical phases of nervous diseases beginning with peripheral nerves, then the cranial nerves, spinal-cord diseases, brain diseases, the various forms of functional disease, and finally the general diseases. There is a very interesting closing chapter on craniocerebral topography and an appendix in which is given the functional innervation of the muscles. The book is freely and well illustrated, although there is not as free a use of charts as there might be. It is needless to discuss the treatment of the subject matter, for any work by Dr. Dana is bound to be first class. No work ever reaches an eighth edition unless it is well worth while.

T. H. W.

HOSPITALS AND THE LAW. By EDWIN VALENTINE MITCHELL, LL.B., of the Faculty of the College of Law, University of South Dakota. Pp. 178. New York: Rebman Company, 1915.

PROFESSIONAL literature grows so rapidly that it is becoming more and more impossible for one to keep in touch with even that of his own vocation; much less is it possible to know the literature of the other professions. Yet the activities of the various call-

ings are so interrelated that every well-informed member of each must know something about the others. This is especially true as between the law and medicine. For most of us it can be accomplished only through summaries of the important and well-established facts bearing along the particular lines in which one is interested. Such a summary is this presentation of Dr. Mitchell's. He has brought together the essential legal practices in relation to hospitals and has so served to make possible for the physician and others an understanding of those practices without the necessity of a prolonged search in legal literature.

The book is well written, concise, sufficiently indexed, and gives references to rulings and decisions upon which its statements are based. It will be found most helpful to those interested in hospital management. T. G. M.

A GUIDE TO GYNECOLOGY IN GENERAL PRACTICE. By COMYNS BERKELEY, M.A., M.D., M.C. (Cantab.), F.R.C.P. (Lond.), Obstetric and Gynecological Surgeon to the Middlesex Hospital and Surgeon-in-Charge of its Military Hospital at Clacton-on-Sea; Surgeon to the Chelsea Hospital for Women; Senior Obstetric Surgeon to the City of London Lying-in Hospital, etc., and VICTOR BONNEY, M.S., M.D., B.Sc. (Lond.), F.R.C.S. (Eng.), M.R.C.P. (Lond.), Assistant Obstetric and Gynecological Surgeon to the Middlesex Hospital and Surgeon-in-Charge of its Military Hospital at Clacton-on-sea; Surgeon to the Chelsea Hospital for Women and the Hounslow Hospital, etc. London: Henry Frowde, Oxford University Press; Hodder & Stoughton, Warwick Square, E. C.

THIS volume is constructed along lines entirely different from those which we are accustomed to expect in text-books, since the sole aim of the authors has been to demonstrate the *significance* of symptoms and the *interpretation* of physical signs. To this end they have divided the book into five sections. In the first section the various methods of examination of patients and the more common instruments used in such examinations are briefly but clearly considered. The second section is devoted to the consideration of symptoms as such, each symptom being carefully considered in its relation to the various conditions in which it might be found, while disease entities are not considered *per se*. Thus, for example, a fibromyoma of the uterus is not described as a separate clinical condition, but is classified under various headings such as uterine hemorrhage, menstrual pain, sterility, etc. The third section of the book deals with physical signs in a similar manner, and it is this "cross-index" feature of the book that renders it of especial value to the practitioner and student. The treatment of the various conditions described form

the fourth section of the book, but operative technic has been deliberately omitted. In this section many practical suggestions are offered, including the publication of prescriptions which the authors have found of service in their wide experience. A bit of conservatism is inferred concerning the value of radium in the treatment of carcinoma of the cervix, and it is surprising to note that early operation is recommended in gonorrheal salpingitis and that phylacogens are suggested in the treatment of chronic gonorrhea. The final section of the book is devoted to the medicolegal aspects of gynecology according to the laws of England, embracing such topics as nullity of marriage, rape, criminal abortion, foreign bodies left in the uterus, vagina, or abdomen, etc.

As a whole, the book is one which should be in the hands of every practitioner who attends gynecological cases, and the numerous semidiagrammatic illustrations and conciseness of the text should render the work especially appealing to the student. F. E. K.

ABDOMINAL INJURIES. By PROF. RUTHERFORD MORISON and LIEUTENANT-COLONEL W. G. RICHARDSON, R.A.M.C. (T.). Pp. 116; 16 illustrations. London: Oxford Medical Press.

THE book is written by Rutherford Morison. Colonel Richardson's name appears by reason of the diagrams which are of little value. The author states that there is no essential difference between the surgical principles which should guide civil and military surgeons. The bulk of the volume is made up of a description of operative technic and postoperative complications and their treatment which differs essentially from the ordinary text-books. The subject of diagnosis is well presented. A few pages are devoted to general considerations of penetrating perforating and gunshot wounds. G. M. L.

WOUNDS IN WAR. THEIR TREATMENT AND RESULTS. By LIEUTENANT-COLONEL D'ARCY POWER, R.A.M.C. Pp. 104. London: Oxford Medical Press.

THE American surgeon who seeks the knowledge already gained by the combined experience of many military surgeons will be disappointed in this book. It is truly a "primer." The general principles of suppurating wounds in their various aspects are discussed with special reference to antiseptic methods, but the treatment of specific infections such as tetanus and gaseous gangrene is superficial and incomplete. G. M. L.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

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Proteose Intoxication.—G. H. WHIPPLE (*Jour. Am. Med. Assn.*, 1916, lxvii, 15) reports further findings in his study of proteose intoxication which develops in intestinal obstruction, general peritonitis and acute hemorrhage pancreatitis. He and his co-workers have demonstrated experimentally that the intoxication of intestinal obstruction is due to a primary proteose which may be precipitated by five volumes of 95 per cent. alcohol or by half saturation with ammonium sulphate. They have found that the proteose is resistant to digestion by intestinal mucosa and by pancreatic and tissue ferments. An animal injected with one proteose is found to be resistant not only to this proteose but also to other proteoses. The toxic proteoses isolated from the intestine from the peritoneum and from the pancreas have certain biologic reactions in common but give no specific differential reactions. Proteoses may be formed in the experimental animals independent of bacterial action. COOKE, RODENBAUGH and WHIPPLE (*Jour. Exp. Med.*, 1916, xxiii, No. 6) have shown that there is a considerable rise in non-coagulable nitrogen in the blood in many conditions of intoxication, especially in acute intestinal obstruction. Without impairment of renal function, the non-coagulable nitrogen may increase from 25 mg. to 100 or 200 mg. per 100 c.c. of blood. Acute proteose intoxications due to the injection of a pure proteose into a normal dog may show a rise in non-coagulable nitrogen in the blood from 25 mg. to 40 or 60 mg. within three or four hours. To throw light on this observation, dogs have been kept in metabolism cages during starvation until the elimination of urinary nitrogen has become constant (usually four or five days). If, now, a small dose of pure proteose is given intravenously, there will be a great increase in the

urinary nitrogen excretion (100 per cent. or more), which may last three to five days. It seems clear that this nitrogen increase must result from tissue catabolism. Animals kept in the same way also show a great rise in the nitrogen elimination if a closed loop of intestine is produced. The authors have produced "a certain type of simple duodenal obstruction" with which there is little or no vomiting and no dehydration. In such cases animals may show over 200 per cent. increase in urinary nitrogen, and death in six to eight days, with a blood non-coagulable nitrogen well over 100 mg. per 100 c.c. Results quite similar to those in intestinal obstruction have been obtained in general peritonitis both septic and sterile, and in acute hemorrhagic pancreatitis, showing that there is a definite proteose intoxication in these conditions.

A Cause of Ascites.—C. F. HOOVER (*Jour. Am. Med. Assn.*, 1916, lxviii, 12) reports some clinical observations which are of interest in connection with the development of ascites. As the author points out, the cirrhotic changes in the liver itself are insufficient to explain the development of ascites, for cirrhosis of extreme grade may be present without accumulation of fluid in the peritoneal cavity. Again, it happens rather infrequently that a patient with cirrhosis of the liver will develop ascites, which may subsequently disappear for months or longer. Recently, Hoover had under observation a patient with alcoholic cirrhosis of the liver. Three weeks before admission to the hospital he had complained of swelling of the feet, legs and abdomen. He stopped work and quit drinking alcoholics, and the swellings disappeared, whereupon he resumed both work and drinking. The swellings again returned and he became jaundiced. The patient had a firm, enlarged liver. There was a caput medusæ over which there was a palpable thrill and a loud venous hum. Systolic blood-pressure was 130, diastolic 90. Eight liters of clear yellow serous fluid were removed. Its specific gravity was 1.005, albumin 4.5 gms. per liter and cell count 180 per 1 cmm. Within a few days, the patient began to improve, the jaundice diminished, and the swelling of the liver subsided. With these changes in the patients condition, there was no alteration in the systolic and diastolic blood-pressures and no visible change in the caput medusæ. It was found, however, that the venous thrill and the murmur had disappeared, a fact which the author ascribes to a lowering of the portal pressure, coincidental with decrease in size of the liver. The findings in this case, together with other clinical observations, lead the author to believe that swelling of the liver is a cause of elevation of portal pressure and that increase of portal pressure is an important factor in the development of ascites of hepatic origin.

On the Reaction of the Cerebrospinal Fluid.—S. H. HURWITZ and C. L. TRANTER (*Arch. Int. Med.*, 1916, xvii (Part I), 828) have made a study of the reaction of the cerebrospinal fluid, as determined by the colorimetric method of Levy, Rowntree and Marriott. The technic for the application of this method to the spinal fluid directly is given. The technic is so simple that the authors consider it applicable as a coutine procedure in examinations of cerebrospinal fluids. The authors summarize their findings as follows: As determined colorimetrically,

normal cerebrospinal fluid is more alkaline than blood, the difference in the hydrogen ion concentration of the dialysates of the two fluids being equal to 0.45, the value of pH for cerebrospinal fluid being 8.11; value of pH for blood, 7.66. No alteration from the normal reaction has been noted either in the blood or in the fluid of patients suffering from primary or secondary syphilis or from syphilitic affections of the nervous system. Thus far, no study has been made of the reaction of the cerebrospinal fluid in acute inflammatory conditions of the meninges.

The Etiology of the Diseases of the Circulatory System.—JANEWAY (*Boston Med. and Surg. Jour.*, 1916, clxxiv, 925) has attempted, in this article, to advance our knowledge of the ultimate and contributory causes of diseases of the circulatory system, with the aim of stimulating wide-spread efforts to reduce their prevalence, for reliable figures, brought forward especially by Bouldan, show a definitely increasing incidence of diseases of the heart, arteries, and kidneys. The author has been able to draw certain logical conclusions as the result of his analysis primarily of the etiological factors concerned in cardiovascular disease. Eleven etiological categories are presented as follows: (1) Diseases due to known bacterial infections; (2) probable, but improved bacterial infections; (3) syphilis; (4) rare infections; (5) parasites and tumors; (6) intoxications; (7) nutritional disturbances; (8) mechanical disorders; (9) nervous disorders; (10) developmental defects; (11) hereditary disease. The author leaves little doubt as to the possibility of reducing the mortality from circulatory diseases. The measures, in order of their importance, best calculated to secure the result, are: (1) A reduction in the incidence of syphilis in association with better diagnosis for and more intensive treatment in the primary stage; (2) reduction of preventable infectious diseases; (3) public education to regard "rheumatism" as a serious malady to be seriously treated, even in mild cases, by the medical profession. In addition to these, Janeway further suggests the establishment of convalescent hospitals for the protracted care of cardiac cases, combined with the development of employments adapted to the limitations of various types of cardiac cases, the promotion in general of good hygiene, temperance, and the periodic medical examination of the presumably healthy. "The need of the moment, therefore, is for more knowledge; not more knowledge of the dangers of circulatory diseases for the public which means propaganda, but more knowledge of their causes for the physician, which means ceaseless investigation."

A Case of Acute Hodgkin's Disease.—WHITTINGTON (*Quart. Jour. Med.*, 1916, ix, 83) presents a case most interesting, by reason of the peculiar course and many difficulties in establishing a diagnosis, which was made certain only by autopsy. The striking features in the case are noted as follows: (1) The onset was acute and with signs and symptoms most suggestive of peritonitis. (2) The patient subsequently suggested typhoid fever with low delirium, apathy, dicrotic pulse, diarrhea, leukopenia, and splenic enlargement. (3) There was a curious periodicity not merely of the fever but of the signs and symptoms as well. Each period of fever marked the initiation of emaciation, rapidly developing pallor, and progressive splenic enlargement; during

each afebrile period the spleen seemed to shrink. (4) There were pronounced signs of portal obstruction. (5) There was no enlargement of the external glands. (6) The blood showed a chlorotic anemia, a leukopenia of 3000, and no eosinophilia. On section the spleen was found much enlarged, as well as the retroperitoneal, portal, and thoracic glands. Histologically these showed the typical appearance of Hodgkin's disease, though the degree of connective-tissue proliferation was not far advanced. This fact and the occurrence of hemorrhagic areas in the glands fits in with the acutely fatal course of the disease. The whole case seems strongly to support the view that Hodgkin's disease is due to some infectious organism, at times much more virulent than at others.

SURGERY

UNDER THE CHARGE OF

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A Simple Technic for Intravenous Injections in Infants.—MARTIN (*Brit. Med. Jour.*, July 8, 1916, p. 40) says that on account of the small size and inaccessibility of the superficial veins in young infants, it is usually difficult, and often impossible, to give intravenous injections or even to obtain sufficient blood for the Wassermann reaction by the methods ordinarily employed. The difficulty is satisfactorily overcome by puncturing the superior longitudinal sinus through the anterior fontanelle, according to the procedure of Helmholtz. The following technic of the method is based on a series of 50 cases: The scalp over the anterior fontanelle is shaved and disinfected with iodine. No anesthetic is required. The child lies in bed with its head raised to a convenient angle on two pillows. A nurse holds the head securely with a hand on either side; the operator stands in front and on the right side of the child. The needle (held at an angle of about 50 to 60 degrees with the plane of the fontanelle) is inserted in the median line, half-way between the anterior angle and centre of the fontanelle. Some little force is required to push it through the firm pericranium, and when the resistance is overcome, one can feel that the point of the needle is in a cavity. The point should not penetrate more than one-eighth of an inch below the surface of the skin since the sinus lies immediately under the pericranium. If the needle is in the sinus blood flows at once into the syringe; should this not happen the needle has gone too deep, and has passed completely through the sinus. This is the mistake usually made by a beginner; it does not, however, cause any damage. The sinus is in many cases so shallow that an ordinary long pointed needle pierces the inner wall before the entire opening in the end of the needle is through the pericranium. A needle of size No. 20 or therabouts,

with a bevel measuring 2 mm., should be chosen in place of one with an ordinary bevel, which measures about 4.5 mm. Autopsies on patients in whom, for diagnostic of therapeutic purposes, the sinus has been punctured at intervals of from a few hours to several weeks before death, showed that in no case had any injury been done, nor in any case in which this method has been used have any untoward symptom followed.

Death After Nitrous Oxide-Oxygen Anesthesia.—McCardie (*Brit. Med. Jour.*, July 22, 1916, p. 109) says that in a somewhat large experience of nitrous oxide and oxygen anesthesia, with and without the addition of ether, he has never seen any other case like this one. The patient very nearly died during the operation and succumbed two hours and a half later without recovering consciousness. The operation, gastro-enterostomy for simple ulcer, was done in a thin, anemic, nervous man, aged sixty-six years, who was considered to be a good subject for nitrous oxide and oxygen anesthesia. The anesthesia lasted thirty-five minutes during the last fifteen of which hardly any gas was given but a good deal of air, and a large quantity of oxygen with rebreathing. There was no respiratory obstruction at any time. McCardie suggests the following points for consideration: That the circulation failed long before respiration. The failure could not have been due to traumatic shock, because it began before incision. The morphine could not be incriminated, because the patient had had as big or bigger doses before, and was not drowsy before operation. There was no asphyxia from obstruction to respiration and twice as much oxygen as is usually necessary was inhaled, while very little gas was given. McCardie does not think that death was due to too much gas, because circulatory failure occurred very early, beginning with the administration of the gas. The patient was psychically a very curiously nervous man, and McCardie thinks that psychic shock, together with anemia, causing heart weakness were largely responsible for the fatality. He admits, however, that this explanation is hardly satisfactory.

The Treatment of Hemorrhoids by Interstitial Injection.—Bird (*Lancet*, July 22, 1916, p. 149) says that some years ago, he chose this treatment for hemorrhoids in himself for the following reasons: The prospect of complete relief in eight or nine visits, each taking a quarter of an hour; very slight pain of no duration; and at the same time no interference with his ordinary work and life. The only change that he noticed in the parts treated was an appreciable, but very slight, warmth. He is still perfectly comfortable. Pure carbolic acid as an injection into pile tissue was first used in the United States about half a century ago, but through misuse the practice fell into abeyance. Some thirty years ago it was resumed in a mitigated form by Dr. Hoyt, of New York. The deviations from his treatment in many hands seemed to have caused disappointment, perhaps through seeking more rapid or more complete success. There is no stretching of the sphincter and no confinement to bed. The solution for injection consists of equal parts of hazeline and distilled water, to which is added 10 per cent. of pure carbolic acid; the whole of the acid is not dissolved unless warmed; the bottle must be shaken when the solution becomes turbid from the

finely disseminated acid, and is then ready for use. It should not be allowed to run on mucous membrane or skin, as in both cases it gives rise to soreness. Bird has had no trouble with carbolic acid absorption, though he has injected as much as 15 mm. at one sitting. The treatment has, at least, two disadvantages: the number of visits, and the passage of the anal speculum. He has found the best speculum to be Kelly's sphincteroscope, both for the first examination and the ensuing treatment, but it should always be well warmed before insertion and well lubricated. He has had made for himself a self-retaining speculum, as Kelly's requires one hand to retain it during the injection by the other. It is better not to inject a pile near the junction of the mucous membrane and the skin or external to that line before the inner or upper portions have been treated. External piles (inflamed) should be allowed to subside under appropriate treatment before injection and the patient should be advised against taking wine, spirits, and highly seasoned dishes and should be given medicines to produce soft evacuations. A platino-iridium needle not too fine and about an inch and a quarter long is perhaps the best, though he uses a short, stiff, needle on a prolongation that fits on to the Record syringe, as this gives a clear view of the length of the speculum. Care should be taken to keep the needle in the long axis of the bowel and a slight side-to-side motion as the plunger is pressed on tears the interior of the pile, and if the needle is kept in for a few seconds there is seldom any bleeding. After an injection or two the pile surface becomes hard, so that future injections should be made between the old scars until the pile is completely cured. An ordinary pile condition requires eight or ten injections, a commencing pile only one or two. At the first visit, Bird now gives preference to injections of not more than three minims superficially to different parts of the surface of the pile; this makes subsequent injections almost painless and prevents the swelling caused by larger injections made more deeply. Cases with two-day intervals between injections do better than those with longer intervals.

Separation of the Lower Femoral Epiphyseal.—MacAusland (*Surg., Gynec. and Obst.*, 1916, xxiii, 147) reports two of these rare cases and a statistical collection of thirty-six cases collected from the literature. This type of fracture usually occurs from direct violence, such as the catching of a leg in the spokes of a revolving wheel. The deformity is usually a displacement of the epiphysis backward into the popliteal space, the lower end of the shaft projecting its sharp edge forward above the patella. Conservative treatment of such displacement by the inclined plane, or other traction and splinting are useless. Closed reduction under an anesthetic is accompanied by dangers, injury to the popliteal vessels and nerves, and the improbability of obtaining complete reduction. The open reduction is necessary and is not only simple, but should always succeed in giving proper alignment and a clean blood-free joint. The details of operative procedure are as follows: A tourniquet is applied. A lateral incision, usually on the inner side, is carried down to the seat of fracture by blunt dissection, and the accumulated blood-clot thoroughly washed out. With a blunt dissector or other heavy instrument, the lower fragment is pried into place, usually without much resistance and usually with complete

anatomical reduction of fragments. The well-fitted serrations give to the reduction a valued stability and as well insure against the slightest possible injury to the epiphysis. After closure of the wound and removal of the tourniquet, a plaster cast is applied from the groin to the ankle. At the end of one week the plaster is split and a few degrees of motion made without removal of the leg from the posterior shell. This process is repeated gently each day. The plaster is taken off after ten days, and from this time on there may be expected an uneventful convalescence.

THERAPEUTICS

UNDER THE CHARGE OF

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Epilepsy, with Special Reference to Treatment.—Dercum (*Jour. Am. Med. Assn.*, 1916, lxvii, 247) says that the first indication in the treatment of epilepsy is that the patient, though defective and deviate, should lead as physiological a life as is compatible. To attain this end a life without physical or mental strain, close to nature, in camp or on the farm, should be adopted by the epileptic. This, indeed, is the principle applied in the various epileptic colonies. In a given number of cases it is attended by an improvement in general health and a notable diminution in the number of seizures. There can be no doubt that the benefit is largely due to the increased oxidation of waste and toxic substances and the general increase of physiological efficiency which result from an outdoor life. In addition three points should be borne in mind: The diet should be so modified that in this organism, already toxic, as little strain as possible be placed on the liver, the thyroid, and other defensive glands. For this reason the red meats are to be partaken of sparingly. The carbohydrates also are to be diminished. To take the latter in large amount is to hamper the oxidation of the tissues, an oxidation which for the obvious reason of the autotoxicity of the patient should be maintained at as high a level as possible. In the diet, emphasis should be laid on the white meats, the succulent vegetables, and milk; eggs also may be permitted. Stimulants of all kinds are, of course, to be excluded. The various avenues of elimination should be kept freely open. If the diet does not of itself counteract the constipation frequently present, a moderate dose of a simple saline or laxative water may be given daily. The patient should drink water freely between meals to promote the action of the kidneys, and should take a luke-warm sponge bath daily to promote the action of the skin. The bath should not be such as to promote an active reaction, but merely to favor elimination. Resort to medicine must, of course, be had in many cases to influence or control the seizures. Time will not permit the extended discussion of these, but after all is

said and done, experience teaches that chief reliance must be placed on the bromides. Regarding their efficient administration, however, one important point must be borne in mind, namely, the principle of sodium chloride withdrawal introduced by Richet and Toulouse. If table salt is withheld, the bromides instead of being eliminated are retained, and are effective in much smaller dose. Dercum has been in the habit, for many years past, of administering the bromides in the form of sodium bromide, at the same time instituting as rigid a withdrawal of the sodium chloride as possible. There can be no doubt that under these circumstances the sodium bromide takes the place, in a measure, of the sodium chloride in the tissues. If in a case so treated the sodium bromide be discontinued and sodium chloride resumed, the bromide is rapidly eliminated in the urine. But one other point of importance remains. In a given number of instances the physiological level of the patient may be distinctly raised by the administration, from time to time, of small doses of thyroid extract; from an eighth to a quarter of a grain, three times daily, seldom more. Thyroid in small doses, long continued, stimulates the chain of glands of internal secretion, increases oxidation, and promotes metabolism generally.

Studies on a Case of Bichloride Poisoning.—Lewis and Rivers (*Johns Hopkins Hosp. Bull.*, 1916, xxvii, 193) say that the necessity of prolonged and vigorous treatment of every case of bichloride poisoning cannot be too strongly emphasized. Many apparently moribund individuals have been saved by properly directed and vigorously pushed therapeutic measures. Death should be the only indication for a discontinuance of treatment prior to the complete recovery of the patient. Retention of waste nitrogen is undoubtedly a factor in the early fatal issue of these cases. There are rarely any signs of uremia. The protein sparing powers of the carbohydrates are of the greatest value in delaying the appearance of the extreme grades of nitrogen retention which usually precede death. If carbohydrates cannot be retained by mouth, glucose may be given intravenously in a 10 to 50 per cent. solution. In addition to its protein sparing action the glucose itself acts as a mild diuretic. It is probable that alkalis have a decidedly beneficial action. Macnider has recently pointed out that they are capable of protecting the kidneys from the full effects of uranium intoxication. It is possible that large doses of sodium bicarbonate given intravenously soon after the taking of the poison would exert a similar protective action in bichloride poisoning.

The Treatment of Paralysis Agitans with the Parathyroid Gland.—Berkeley (*Med. Record*, 1916, xc, 105) says that further experience seems to justify the opinion that the administration of the parathyroid glands does not assure a "cure" for paralysis agitans, but asserts that from 60 to 70 per cent. of the patients treated by this remedy have been greatly benefited, and that in such patients the progress of the disease has been arrested or very materially retarded. The author believes that much the best preparation of the parathyroid gland is an acetic acid extract of the fresh glands (commonly, though very inaccurately, called a "nucleoproteid" extract) made by treating the

ground or triturated glands with cold distilled water, filtering, and then precipitating with very minute amounts of acetic acid. This extract is now prepared commercially, and may be obtained without great expense. Berkeley uses this extract in doses of one-fortieth of a grain either by mouth in a capsule with milk-sugar or hypodermically in a solution. The solution is given in doses of 15 minims, and, if it is injected with reasonable care, produces no local effects of a disagreeable nature. The article by Berkeley is not entirely convincing but very enthusiastic about the success of the parathyroid treatment in "hundreds of cases."

Arsenobenzol in the Treatment of Syphilis.—Ormsby and Mitchell (*Jour. Amer. Med. Assn.*, 1916, lxvi, 867) write concerning arsenobenzol which is an arsenic preparation manufactured in America as a substitute for salvarsan. The authors gave 184 injections to 75 patients suffering from syphilis in its various stages and believe that some conclusions as to the value of this remedy can be drawn. Its action has been uniform, its toxicity low, and its therapeutic results have been excellent. The immediate reactions have been almost negligible, and remote untoward results entirely absent. They employed it in both early and late cases, including those with primary lesions before eruptive manifestations have occurred; in the so-called secondary and tertiary stages; also in latent cases, and those involving the cerebro-spinal system. The authors give the detailed method of the preparation of the solution of the drug for intravenous injections. The preparation of the solution and the intravenous administration are very similar to that of salvarsan. In their conclusions Ormsby and Mitchell state that arsenobenzol, together with mercury, offers as good a method of treatment of syphilis as any heretofore used. In its uniform and non-toxic action, arsenobenzol commends itself as a remedial agent of great value in the treatment of syphilis, and its successful preparation marks an achievement in American chemotherapy. While a sufficient experience has not as yet been had from which to draw ultimate conclusions, they believe its therapeutic accomplishments, together with its safety of administration, recommend its continued employment.

The Reactions and Results of Treatment in Cerebrospinal Syphilis.—Draper (*Jour. Amer. Med. Assn.*, 1916, lxvi, 400) has made observations on 38 cases, watched over periods of from three months to three years. These 38 patients were given 1126 intravenous injections and 355 intraspinal injections of medicated serum. The technic of administration was the usual one. He found that the severest reaction to intravenous injections was of the anaphylactic type. The most frequent reaction to the intraspinal injections was pain. The severest was an aseptic meningitis, which might have been anaphylactic in origin. Twenty-six patients out of the total of 38 were economically useless before treatment. After treatment 22 were back on full time work. The rapidity and degree of improvement depended directly on the intensity of the treatment. Draper emphasizes the importance of keeping the patients at work on part time at least during the months of treatment in order that their period of disability may be shortened.

The Treatment of Pneumonia with Ethylhydrocuprein (Optochin).—LOEB (*Berlin. klin. Wchnschr.*, 1915, lii, 1108) reports his results in the treatment of pneumonia with optochin. He believes that the remedy, to be effective, should be given early, as soon as chill, fever, pains in chest and cough have appeared without waiting to make the diagnosis certain. The effect of the remedy is seen principally in a critical fall of the temperature usually on the day following its administration. The crisis may be a true one but as a rule there is a return of the fever and it is necessary to repeat the remedy. The results reported are favorable. Occasionally toxic symptoms resembling those due to overaction of quinine are produced by optochin, but these symptoms disappear promptly if the remedy is withdrawn for twelve to twenty-four hours.

The Local Treatment of Meningeal Syphilis.—ZENNERICH (*München. med. Wchnschr.*, 1915, lxii, 1696) sees no especial advantage in intraspinal administration of salvarsanized serum as compared to injections of small doses of salvarsan itself. He does not state this as a proved fact as he says that later and more complete reports may modify this view. In the term meningeal syphilis Zennerich includes cerebrospinal syphilis and also metaluetic infections. He emphasizes that treatment must be begun early in these syphilitic affections in order to secure results. He does not believe that the ordinary combined treatment, salvarsan and mercury, as applied to constitutional syphilis can exert any influence on meningeal syphilis. Intraspinal injection of salvarsan must be given with great caution, for too concentrated solutions may cause an increase in symptoms and may even produce a myelitis.

Strontium Salicylate.—BLANKENHORN (*Jour. Amer. Med. Assn.*, 1916, lxvi, 331) says that salicylate of strontium has had a therapeutic reputation for which there is no satisfactory foundation discoverable. The chief advantage claimed for strontium salicylate as compared with sodium salicylate is that the strontium salt gives rise to fewer unpleasant by-effects, particularly digestive. The author endeavored to determine if strontium salicylate differed from sodium salicylate either as regards therapeutic efficiency or undesirable by-effects. The drug was easily given in all cases, and no more than the usual protest was made about the taste. Strontium salicylate is only slightly soluble in water and hence must be given in powder form which is less convenient and less accurate than the use of a stock solution of sodium salicylate. He found that strontium salicylate in comparable doses produced the same gastric and other toxic symptoms produced by other salicylates. No difference in therapeutic efficiency was observed. The fact that strontium salicylate is much more expensive and more inconvenient to give than sodium salicylate also helps to destroy the tradition held by some that this form of salicylate is superior to the more common sodium salt.

The Treatment of Paresis and Tabes Dorsalis by Salvarsanized Serum.—COTTON (*Amer. Jour. Insanity*, 1915, and 1916, lxxii, 125, 355, 485), in this article which is continued through three numbers of the

above journal discusses the various methods that have been advocated for the treatment of tabes and paresis. The article includes interesting detailed case reports and tabulation of the results in the individual cases, for which the original article should be consulted. With regard to various methods of treatment Cotton considers from his experience that the Swift-Ellis method is as efficacious as any. The criticism of this method is that it has to be administered too slowly because of the dangers of too frequent intravenous injections of salvarsan. Treatment is thus extended over a considerable period of time before permanent results can be obtained. Consequently Cotton says that he has been combining the Swift-Ellis and Ogilvie methods on alternate weeks with good results. The author believes that the value of mercury and iodide of potassium as an adjunct to salvarsanized serum in the treatment of paresis and tabes is at present an unsettled question. With regard to the use of salvarsan or neosalvarsan there is also considerable difference of opinion. At first Cotton used neosalvarsan exclusively. The general opinion seemed to be in favor of salvarsan, and so the author has used salvarsan during the past nine months. His results were no better than with the neosalvarsan, and in two cases he had a pronounced aseptic meningitis with salvarsan, an experience which never occurred with the use of neosalvarsan. The total number of cases of paresis reported by Cotton was 66 and in all 600 treatments were given. From this number the author selected 31 patients for detailed study who were treated for at least six months, but in all but a very few cases the treatment extended for over two years or the patients have been observed for that length of time. Of this group of 31 patients, 11, or 35.5 per cent. are classified as arrested; 7, or 22.5 per cent. were much improved; 7, or 22.5 per cent. were not improved, and 6, or 19.5 per cent. died. Only 4 cases of tabes are reported occurring in patients from forty-eight to seventy years of age, and no especial conclusions can be drawn from these patients. For his conclusions Cotton emphasizes the fact that in the use of salvarsanized serum we have an agent which does cause definite arrest in paresis, which arrest includes improvement in the clinical symptoms, physical signs and a corresponding change in the biological reactions from positive to negative. To be effective the case must be treated in the early stages, as advanced stages show no favorable reaction to the treatment. The length of time is not always an indication of the severity of the symptoms, but the majority of cases cannot be helped after two or three years have elapsed. Treatment must be persistent and uninterrupted, grading the amount of dose and frequency of treatment to the condition of the patient. Taboparesis should be cautiously treated, usually with small doses and not oftener than every three weeks. The remissions caused by the treatment cannot be compared to spontaneous remission, for the percentage in the former is 35.5 per cent., and in the latter case only 4 per cent. The change in the cell count, globulin content, blood and spinal fluid Wassermann reactions are the direct result of the treatment and not to be compared with the variation found in untreated cases of paresis. The efficacy of the treatment depends not on the method used but on the stage of the disease; hence the necessity for early diagnosis in paresis and prompt treatment as soon as possible.

A Contribution to the Chemotherapy of Tuberculosis.—KOGA (*Jour. Exper. Med.*, 1916, xxiv, 107) writes concerning a preparation of copper and potassium cyanid since named cyanocuprol. The preparation used by Koga is a double salt of copper and potassium cyanid diluted 1 to 2000 and treated in a special manner to prevent the formation of free hydrogen cyanid. He does not state what this special manipulation is, but insists that unless this manipulation is carried out, the injection of the remedy is not safe for human beings. Koga's contribution is divided into two papers. The first deals with the effect of the new remedy in animal experiments, in which over 150 guinea-pigs were used. In his summary of the effect of cyanocuprol in his animal experiments, he says that judging from the macroscopic and microscopic study of the animals its action seems to be about as follows: The effect of a single injection upon the lesions is either negative or inconspicuous. But after rejected injections of the preparation the congestion and leukocytic infiltration about the lesions are markedly decreased, the cheesy material resulting from degeneration of the lesions and other degenerative products are in process of absorption, and young connective tissue is being actively produced in the periphery. While these changes are taking place the number of the bacilli is also being reduced until finally they can no longer be found on microscopic examination. However, the complete disappearance of tubercle bacilli was disproved in some of the animals apparently cured by the treatment. Emulsions were made of the lungs, liver, spleen and other organs of some of the animals, apparently healed, and injected into the peritoneal cavity of guinea-pigs. Such injections were followed in some instances by the development of tuberculosis. Koga's experimental work is supplemented by a clinical report of sixty-three cases of human tuberculosis in various stages treated by the new remedy. Eleven of these cases are reported in detail. The author's conclusions, which seem to be justified by the reports, are "that the preparation greatly improves or apparently cures pulmonary tuberculosis and surgical tuberculosis in the first and second stages, and that it seems also to produce beneficial effects upon the disease in the third stage. The duration of these beneficial effects is still to be established by more numerous trials and many years of observation. The preparation must be given intravenously, and the doses must be increased or decreased according to the age and constitution of each patient. Moreover, it should be borne in mind that the pathological phenomena and the constitution of each patient have much to do with the determination of the dose. The manner of action of the preparation is not yet entirely clear. But if it acts primarily upon the tissues which bear the tubercular lesions and then indirectly against the germ, as he assumes at present, the activity which the tissues exert will have much to do with the efficacy of the preparation. If this hypothesis is correct, according to Koga, the minimum doses (10–12 mg.) will be best suited to a patient who is greatly emaciated, and should be gradually increased as the reactions, pathological processes, nutrition, etc., indicate. In any case, the dose of the preparation must be determined by the condition and constitution of the patient. In animal experiments he says that he has been fortunate enough to obtain results which no other preparation has given. The clinical application and the establishment of its full efficacy in human cases must be left to the physician.

OBSTETRICS

UNDER THE CHARGE OF

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Transperitoneal Cellohysterotomy.—POLAK (*Am. Jour. Obst.*, July, 1916), has performed eight operations by the following method: Incision is six inches long at the right of the median line, below the umbilicus. The peritoneum is opened, the uterus pushed into the wound, the bladder and visceral peritoneum separated, and the peritoneal reflection of the uterus and that of the abdominal wall and the visceral and parietal layers are united by sutures. An interrupted figure-of-eight with catgut, leaving the ends long, is used. These sutures unite the two layers of the peritoneum and make the lower uterine segment extraperitoneal. To avoid the tearing of the suture at the upper angle the uterus is sutured to the peritoneum and fascia, thus fixing it at the upper angle. After the uterus is emptied the wound in the uterine muscle is closed with interrupted sutures of chromic catgut. When infection is present a gauze pack soaked in iodin is placed in the uterus and removed through the cervix and vagina at the end of the operation. After closing the uterus the operator closes the peritoneum with continuous sutures. The results in his eight cases have been satisfactory.

The Care of the Pregnant Woman.—DONALD (*Brit. Med. Jour.*, July 8, 1916) believes that the pregnant woman must be taught how to take care of herself and warned of certain dangers that may arise. Those agencies which will give her needed information should be encouraged, such as schools for mothers and other means of education. The practical and theoretical training of midwives should be greatly improved, and a routine examination of the urine must be insisted upon. Improvement in medical education of students, with practical training, is most important, and a residence in a maternity hospital for several weeks is essential. Postgraduate instruction for medical practitioners must be provided, and especially such facilities as will enable them to live in a maternity hospital and receive proper clinical training. Methods of diagnosis, aseptic precautions, and the general treatment of confinement cases must be thoroughly taught. Clinical laboratories in connection with maternity hospitals are essential to study those problems most important in connection with abortion and stillbirth. Maternity hospitals must be provided throughout the country under the charge of obstetricians of experience, who should act as consultants in all difficult cases. Medical officers of health and boards of health and examining boards must coöperate in bringing about these improvements.

Editorial Comment on the Care of the Pregnant Woman.—The *British Medical Journal* for July 8, 1916, considers DONALD'S paper of sufficient

importance to merit editorial comment. Donald's statement that the solution of the matter, namely, the care of the pregnant woman, is not in statistics and notification, but in education and research, is endorsed by the editor. It is acknowledged that medical education in the department of obstetrics should be greatly improved and that clinical facilities and methods of clinical training should take precedence. So far as the care of the pregnant woman and successful production of healthy children is concerned, an important element in the problem lies in the effort to secure bounties given by the state for this purpose. Picard's opinion is quoted that there must be a bonus for every child, and that the birth of another child must not impoverish the family. This in France has amounted to about $20. The editor of the *British Medical Journal* does not pretend to say what the real remedy is in this matter of financial aid for the production of children. He states that it is the greatest problem of the immediate future. There are objections to a great increase in wages, and there are some reasons to hope that an improvement in housing conditions may be of service. The editor does not believe that notification of cases of pregnancy will be of much service, but he cannot escape the opportunity of taking a fling at German Kultur and the German methods of state control.

Syphilis in Relation to Obstetrics.—At a recent meeting of the American Gynecological Soliety, May, 1916, a number of papers upon this subject were contributed. DAVIS presented a paper reviewing the progress of obstetric science since the discovery of Spirochete pallida and salvarsan. He calls attention to the fact that a practically positive diagnosis can now be made by the discovery of the germ in the tissues of the umbilical cord or the blood from the umbilicus. Latent syphilis is of great importance, as it explains the apparent immunity of the nursing mother toward her syphilitic child. Such a patient, however, is syphilitic, and must be so considered and so treated. While salvarsan is of great value in checking the most acute and virulent stage of syphilis, its use in pregnant women may be followed by abortion, and for a definite and permanent result for mother and fetus, it is inferior to mercury and iodide of potassium. In the present stage of obstetric science we have gained greatly in certainty of diagnosis in the detection of obscure cases, especially those of tertiary syphilis when luetin is of value. We have gained in the treatment of syphilis in its acute stage more than in the other stages. The Wassermann reaction, like the Abderhalden test for pregnancy, is misleading in many conditions, and is not to be relied upon for diagnosis or treatment. When the question of the marriage of syphilitic persons arises, at least six years of thorough treatment and observation are necessary to be reasonably sure of recovery. Repeated negative Wassermann reactions by no means prove that absolute recovery has occurred. GELLHORN and EHRENFEST contributed a paper reviewing a series of cases which they had carefully collected and analyzed from a literature and from their own experience, and the paper is illustrated; in its accurate thoroughness it is a valuable acquisition to obstetric literature. In discussion Williams estimated that 26 per cent. of deaths of children after the first two weeks of the puerperal period were due to syphilis. Among negroes syphilis is four or five times more common than in the whites. Buhman gave the results of his study of various

diseases, malignant and otherwise, by the Wassermann reaction. With a few exceptions a strong positive Wassermann reaction very accurately controlled and carefully made is conclusive evidence of syphilis. A weakly positive reaction without clinical evidence of the disease was unreliable. Syphilitic infection might be present with a negative reaction. So far as the observation went, malignant diseases did not give a positive Wassermann reaction. Peterson drew attention to the uncertainties of diagnosis from clinical symptoms alone and histories. Of 290 gynecological patients, 5.6 per cent. gave positive Wassermann reaction. Among these 22 patients but 5 gave a history of syphilis. The frequency of syphilis in women coming to a clinic for obstetrics and gynecology is about 5 per cent. In a mixed hospital it is from 8 to 10 per cent. ADAIR had studied the relation of syphilis to miscarriage and fetal abnormalities. Apparently pregnancy did not end much more frequently during the first three months in those affected with syphilis than in those who were free from the disease. Among premature births there was evidence of syphilis in about one-third of the mothers. Congenital syphilis appeared in 105 of infants born in the hospital. Of 50 premature infants 8 were syphilitic. SLEMONS had found that accurate diagnosis of syphilis in obstetric patients requires the use of both the Wassermann reaction and the study of the placenta. The freshly teased chorionic villi should be examined in every case. If their appearance raised a suspicion of syphilis the placenta must be hardened and studied, and a Wassermann reaction taken with the mother. BAESLACK had studied the question of the relation of the germ to syphilis by experiments upon animals, and believes that this is practically established. C. C. NORRIS reported a case in which he had diagnosed syphilis of the body of the uterus. TAUSSIG had studied syphilitic fever and found that a diagnosis could rarely be made with absolute certainty. Secondary syphilitic fever occurs in a mild form in 20 per cent. of syphilitic patients at the outbreak of the eruption, and sometimes is prolonged and severe. Late secondary syphilitic fever is occasionally seen after confinement or operation. Tertiary syphilitic fever is practically never due to syphilitic lesions in the female genital tract. Apparently this fever is caused by the reaction of the body to the toxins produced by the germ of syphilis. ANSPACH, in 300 patients, gynecological and obstetric, found a positive Wassermann reaction in 22.6 per cent. In cases of stillbirth cases of positive reaction was obtained in 75 per cent. In rectal disease in 50 per cent.; in abortion in 43 per cent.; in pelvic inflammatory cases in 36 per cent.; in fibroid tumors of the uterus in 16 per cent., and in cases of pregnancy in 17 per cent. In the negress syphilis is more common than in the white. FOULKROD described a case of syphilitic fever where salvarsan was given once followed in ten days by the return of fever. A second dose ended the attack.

Cesarean Section for Accidental Separation of the Placenta.—MAYNE (*Am. Jour. Obst.*, 1916, lxxiv), was called to a woman, seven months pregnant, suffering from vaginal hemorrhage. This was but partly controlled by packing, the cervix was small and tightly closed, and the patient was delivered by section. The placenta was almost completely detached and there was a quart of blood and clots in the uterine cavity. The patient made a good recovery.

GYNECOLOGY

UNDER THE CHARGE OF

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Iodine Treatment of Pruritus Vulvæ.—The following simple treatment for pruritus vulvæ is warmly recommended by HEUSLER-EDENHUIZEN (*München. med. Wchnschr.*, 1916, lxiii, 564) who claims excellent results. In cases with no visible skin changes and with little or no leucorrhea the vulva is thoroughly cleansed as for a vaginal operation, dried, and then painted with a 10 per cent. tincture of iodine. The patient is instructed to exercise the most scrupulous cleanliness; in some cases one treatment suffices, but if necessary it may be repeated. In more advanced cases, with skin changes, such as reddening, swelling, fissure-formation, induration, etc., and more or less severe leukorrhea, every effort should be made to keep the vulvar region dry and free from the vaginal secretion. For this purpose the author uses the dry powder treatment for the vagina, by means of insufflation of zinc oxide or lenicet powder. Externally, the 10 per cent. iodine solution is used followed by dusting with the zinc oxide or lenicet powder. On about the third day the patient returns, when the entire treatment is repeated, then about every fifth day, and at longer intervals as the condition improves, a definite cure usually resulting in about six to eight weeks. The author claims to have healed in this way many cases of long standing, in which the usual ointments, and even *x*-rays, had been tried without avail. The very first application of iodine usually relieves the intolerable itching for a couple of days, but in some cases it produces intense pain, so much so that occasionally an injection of morphine becomes necessary. In most instances this is not required, however, the pain passing off in an hour or so. The author lays great stress on the importance of keeping away all sources of irritation from the vulvar region during the course of the treatment, and especially is the least moisture to be avoided. For this reason the patient is forbidden to bring any water in contact with the genitalia, is directed to avoid sexual intercourse, to keep as quiet as possible so as to minimize perspiration, and after each micturition and defecation to cleanse the parts with cotton soaked in oil, followed by dry cotton to remove all traces of the oil. Three times a day the entire genital region is to be freely powdered by the patient herself. Several case histories are cited to show the effects of the above treatment in refractory cases.

Vaginal Section in Ruptured Ectopic Pregnancy.—In the treatment of the so-called "tragic" cases of ruptured extra-uterine pregnancy, where the necessity for immediate intervention to check hemorrhage is apparent, BABCOCK (*Am. Jour. Obst.*, 1916, lxxiv, 276) believes that less shock to the patient is caused by a rapid vaginal section and the application of a clamp than by the most dextrously performed lapar-

otomy. His technic is briefly as follows: Under light ether anesthesia with the patient in the lithotomy position the posterior cul-de-sac is opened in the median line by a thrust of a sharp pair of scissors; the index-finger of each hand is then introduced through the opening, which by traction is greatly enlarged. The escaping blood is disregarded; two fingers are immediately introduced into the cul-de-sac and swept to each side of the uterus, locating the tubal enlargement. The diseased tube is freed by sweeping the fingers about it, and when thoroughly isolated it is pulled down through the vaginal incision. A clamp is then applied to the tube and ovary close to the uterus. If the patient's condition permits, ligatures may then be applied, but if not the clamp is simply left in place. The tube and ovary may be cut away distal to the clamp, being careful to leave a sufficiently large pedicle to prevent the friable tissues from slipping out of its grasp. Where the patient is *in extremis*, however, nothing further need be done than the application of the clamp, a piece of gauze being packed sufficiently into the pelvis to isolate the clamp from the intestines and to prevent the edges of the vaginal incision from coming together. A second strip of gauze is placed in the vagina, and the patient returned to bed without irrigation or other maneuvers, the blood in the pelvic cavity being left to drain away gradually. The author says that the entire operation may be performed in from three to ten minutes, and the patient goes off the table with the hemorrhage controlled, and with little increase in the preëxisting shock. The clamp is cautiously opened at the end of forty-eight hours, rotated in each direction, and removed. The gauze is removed on the fourth or fifth day, and the patient sits up at the end of a week or ten days. The author says that in the past ten years he has treated 24 patients by the above method without operative death. One patient died two weeks later from pneumonia, but the final results in all others have been excellent. In no instance was a secondary operation necessary.

Sterilization of Women by Cautery-stricture at the Intra-uterine Tubal Openings.—A rather remarkable method for sterilizing patients where definite indications for this procedure exist and laparotomy is contra-indicated has been proposed by DICKINSON (*Surg., Gyn. and Obst.*, 1916, xxiii, 203). It consists, briefly, in causing a stricture at each tubal opening into the uterine cornu by cauterization through the uterine canal. The technic is as follows: The patient is placed in the lithotomy or Sims position, with bladder empty; the cervix is exposed through a Sims speculum and the anterior lip seized and steadied with a tenaculum. About 5 to 10 minims of a 10 per cent. novocaine-adrenalin solution are injected through a Skene pipette into the cervical canal and held under pressure a few seconds. The canal is then wiped with Churchill's tincture or pure carbolic. A sterile uterine sound is then passed into the uterus and turned gently sideways to outline the uterine cavity and find the cornu, an exact note being made of the distance of the latter from the external os. The sound is then withdrawn, and a cautery sound of the same size is bent to the same shape and has its slide pushed up until exactly the same distance is exposed as was measured on the uterine sound. The cautery sound bears on its tip a little spiral or blunt point of platinum which becomes incan-

descent. The switch is turned on and the platinum heated to show that it is working properly; this is then placed against the cervical mucous membrane in plain sight and a count made of the number of seconds required to burn into the tissues sufficiently to bury the platinum wire. The tip is now allowed to cool, and the sound passed into the uterus to the fundus, being turned to find the cornu as previously determined. The current is then turned on for the number of seconds found necessary to produce the burying effect at the cervix. The other cornu may be done at the same time, or at a second sitting. The author describes this as an office procedure; he lets the patient go home in a short time, advising her to keep quiet the rest of the day and the following day if she has any discomfort. The reaction is slight—possibly a little bloody discharge for a few days, and some discomfort at the next period. There occurs on the cervix a slough and then a clean granulating wound that within two or three weeks is healed over. The author considers that the objections to this method of treatment lie chiefly in unskilled attempts, as insufficient cauterization will not produce complete occlusion. Adhesions of the uterine wall at a lower point than the angle might cause a backing up of menstrual blood, with resulting local hematometra or even hematosalpinx. He thinks that hydrosalpinx of mild degree may arise following correct technic, even when the outer ends of the tubes are patulous, but his is of no serious import. The main difficulty lies in the inability to determine in a given case whether absolute sterilization has occurred; for this purpose Dickinson suggests the injection of a silver preparation into the uterus under pressure and Röntgen examination, to determine if the solution flows out through the tubes, a procedure originally proposed by Cary.

Adenomyoma of the Rectovaginal Septum.—Two cases of this interesting condition are reported by CULLEN (*Jour. Am. Med. Assn.*, 1916, lxvii, 402), these being the fourth and fifth cases that he has observed within a comparatively short time, the others having been reported in papers within the past two years. These peculiar tumors develop in the tissue between the cervix and the rectum, and consist histologically of fatty and fibrous tissue, scattered throughout which are numerous glands resembling exactly those of the endometrium, and often surrounded by small islands of cellular tissue resembling the endometrial stroma. Their importance from a clinical standpoint lies in the fact that from their location, density, and fixation, they are nearly always considered malignant, whereas they are in reality at least morphologically benign, and are practically always amenable to radical removal. In addition to his own cases, Cullen has collected from the literature about a dozen additional ones. They may be roughly grouped into four classes, as follows: (1) Small adenomyomas lying relatively free in the rectovaginal septum; (2) Adenomyomas adhrent to the posterior surface of the cervix and at the same time to the anterior surface of the rectum; (3) Adenomyomas gluing the cervix and rectum together and spreading out into one or both broad ligaments; (4) Adenomyomas involving the posterior surface of the cervix, the rectum and broad ligaments, and forming a dense pelvic mass that cannot be liberated. The ages of the patients ranged from twenty-five to fifty-three years, all the cases occurring in women who were still

menstruating. The most pronounced symptom was profuse menstruation, and rectal pain was also a prominent feature in some cases. The treatment advocated by Cullen for these growths depends somewhat upon their condition. Where small discrete nodules exist they may be readily removed through a vaginal incision. Where the growth occupies the posterior surface of the uterus and extends laterally, the ureters should be dissected out carefully and a complete abdominal hysterectomy performed. If the growth is firmly adherent to the rectum, it becomes necessary to remove a wedge of this together with the uterus, and if the lumen of the bowel is greatly narrowed a complete segment of the rectum should be removed, followed by an anastomosis. In desperate cases, such as one that the author experienced, he advises cutting across the sigmoid, inverting and closing the lower end, and making a permanent left inguinal colostomy. At a subsequent operation the uterus, lower portion on the rectum and the broad ligament tissue can then be shelled out as one piece. The author believes that these tumors are by no means as rare as has been commonly supposed, and that closer observation in the future will result in many other instances being recognized.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Pellagra.—The discovery of the presence of small quantities of substances occurring in foods which are essential to the maintenance of health has opened up important problems in diet, with reference to health and disease. These substances are termed vitamins by Funk. They occur in animal as well as vegetable food, in varying amounts. Certain foodstuffs, as polished rice, are extremely poor in vitamins. Others, as meat, are relatively rich in these substances. Beri beri is due to a lack of vitamins, owing to a diet consisting largely of polished rice. Pellagra is presumably also caused by a lack of vitamins.

So far as pellagra is concerned, VOEGTLIN (*Jour. Amer. Med. Assn.*, 1914, lxiii, 1094–1096) concludes that we have to consider: (1) A deficiency or absence of certain vitamins in the diet. (2) The toxic effect of some substances, as aluminum, which occurs in certain vegetable food. (3) A deficiency of the diet in certain amino-acids. The possible relation between aluminum and pellagra was also discussed in a recent monograph by ALESSANDRINI and SCALA (*Contributo unova*

alla etiologia e pathogenesi della Pellagra, Rome, 1914). These investigators claim that colloidal silica contained in drinking water is one of the most important etiologic factors, in as much as they succeeded in producing lesions resembling pellagra in animals fed on water containing colloidal silica. Colloidal aluminum hydroxid or a mixture of colloidal silica and alumina produced the same results. In view of the fact, as first pointed out by Voegtlin, that aluminum occurs in certain vegetable food in relatively large amounts, the work of the Italian authors furnishes additional evidence that aluminum occupies a prominent position in the etiology of pellagra.

The Significance of Bacillus Coli in Pasteurized Milk.—SHIPPEN (*Jour. Am. Med. Assn.*, 1915, lxiv, 16, 1289) concludes that: As observed by De Graef and De Jong, certain strains of B. coli are not killed by a temperature exceeding that commonly used in pasteurization. The thermal death point of this and similar organisms is not a constant quantity but varies for different strains of the same bacterium. In the case of B. coli communis this variation was found to be as great as 13 degrees. The presence of B. coli in pasteurized milk cannot be taken as an index of its improper pasteurization or subsequent contamination.

The Germicidal Effect of Lactic Acid in Milk.—P. G. HEINEMANN (*Jour. Infect. Dis.*, 1915, xvi, 3, 479–486). The statement is sometimes found in the literature on sour milk or buttermilk having a germicidal effect on pathogenic bacteria. It has also been intimated that lactic acid producing bacteria are a protection against infectiousness of contaminated milk, inasmuch as the acid produced by these bacteria is said to destroy pathogenic bacteria. There is, however, little positive evidence to show whether this assumption is true or not. Heinemann has studied the question and reaches the following conclusions: Some acid-tolerant cells of Bacillus coli may survive the presence of 0.6 per cent. lactic acid in milk. B. dysenteriæ, B. typhosus, B. diphtheriæ, B. paratyphosus B, and Spirillum choleræ in these experiments were destroyed by the presence of 0.45 per cent. lactic acid. It is possible that strains of these bacteria exist which are able to resist a greater amount of lactic acid. Acid-tolerant strains of B. coli, B. dysenteriæ, B. typhosus, and B. paratyphosus B may multiply in the presence of quantities of lactic acid which are destructive to the majority of cells. The smaller the initial amount of lactic acid, the more likely is the growth of acid-tolerant strains. Consequently, the slower milk sours, the greater is the danger of pathogenic bacteria surviving. The growth of the test bacteria is influenced to a marked degree by the amount of acid present. Up to a fairly definite amount of acid there is an increase in numbers, followed by a decrease, which becomes more pronounced as the amount of acid increases. The amount of acid may increase after the number of bacteria has commenced to decrease owing to the liberation of enzymes. Acid other than lactic acid are frequently present in buttermilk. Buttermilk therefore should be looked upon with suspicion, especially if heavily polluted, unless prepared from pasteurized milk. Still the chances of buttermilk becoming a carrier of infection are much smaller than of raw sweet milk. The presence of

saprophytic bacteria in buttermilk may have some influence on pathogenic bacteria. Whether this influence is favorable or otherwise, is difficult to determine by present bacteriological methods.

Studies on Immunization through the Nose.—SEWALL and PEWELL (*Arch. Int. Med.*, 1915, xvi, 605) sensitized guinea-pigs to horse serum by dropping it into the nose. They believe that special advantages accrue through the use of this channel of immunization. When serum was dropped upon the nostril to the amount of 0.1 to 0.2 c.c., and the instillation was repeated at intervals of one to twenty-four days to a total of six doses or less, the animal became affected in one of two opposite directions. When an intravenous injection of about 0.4 c.c. of serum was given sixteen days after the last instillation the pig might die in anaphylactic shock. But in about half the cases the animal survived this large toxic injection. Certain individuals not only survived, but manifested no signs of sensitiveness. It would be clear that the latter animals had not abosrbed the serum through the mucous membrane of the nose were it not that they resist subsequent injections separated by intervals of more than three weeks. The object of the present research was to determine the experimental conditions according to which an animal might be made; on the one hand, anaphylactic or, on the other, refractory to a toxic injection of the antigen. The experiments were applied, especially to determine the effect of the number of separate instillations of serum and the length of the intervals between them on the reactivity of the guinea-pig. No definite relation could be found to exist between these conditions, nevertheless a number of peculiar facts were established. A guinea-pig which has been immunized by nasal instillation and then has received a series of intravenous injections so that the animal tolerates, say, 0.4 c.c. serum with slight reaction, where a long resting period, such as three months, is allowed, the resistance to serum is found to have increased so that two or three times that amount may be equally well tolerated though, as proved by controls, the larger dose would have been fatal at the beginning of the resting period. The serum of pigs thus immunized when injected into normal guinea-pigs did not render them anaphylactic but, on the contrary, showed some power to protect them against toxic injections repeated at intervals of two weeks. The offspring of female immunized animals were markedly or wholly refractory to the intravenous injection of horse serum. A tentative hypothesis is drawn from the experiments, namely, that the biologic response to the introduction of an antigen consists in the development of two opposite-acting antibodies. One, the familiar *allergin* or *anaphylactic* antibody, the other an *anti-allergin* or *protecting* antibody. The present communication must be regarded as simply preliminary to further work.

Cancer-like Growths in Rat's Stomach following Irritation.—Fibiger's announcement of the production of carcinoma in the rat's stomach through the agency of nematodes has not as yet been controverted. F. D. BULLOCK and G. L. ROHDENBURG (*Proc. Soc. Exper. Biol. and Med.*, 1915, xii, 161) record the fact that somewhat similar pictures can be produced by other means of irritation.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Bacteriological and Experimental Studies on Gastric Ulcer.—Many studies and experiments have been undertaken to determine the pathological process in gastric ulcer. CELLER and THALHIMER (*Jour. Exper. Med.*, 1916, xxiii, 791), stimulated by the positive results reported by Rosenow, have repeated the work using his technic in isolating and injecting streptococci into rabbits and cats. The bacteria used in the experiments were isolated from the tissues of eight gastric ulcers and one ulcer at the ostium of a gastrojejunostomy. Histological examination of the human tissues showed the presence of organisms only in or upon the lining of the degenerating tissue of the ulcer. Various microörganisms were observed in this situation. In culture streptococci with other bacteria were isolated in 8, while a staphylococcus and Gram-positive bacillus were obtained in 1. Suspensions of the microorganisms obtained were inoculated into the ear vein or a branch of the gastric artery. In 2 cats a branch of the gastric artery was injected with streptococci. Both animals developed defects of the gastric mucosa which soon began to heal and were completely repaired in thirty-three days. Of the 30 rabbits injected intravenously with streptococci, gastric lesions developed in 4, while 14 showed cardiac lesions. In 8 rabbits a branch of the gastric artery was injected with streptococci and lesions developed in 6. The authors are not convinced that the lesions which they observed in their animals were truly gastric ulcers as there lacked the characteristics of those observed in man. The promptness of healing also strengthened the belief that the lesions in animals and man are not comparable. Embolic lesions in the stomachs of cats healed spontaneously and did not appear to be influenced by the presence of streptococci. They conclude that even though anhemolytic streptococci are present in practically all gastric ulcers it has not been proven that these microörganisms initiate the ulceration or prevent healing.

The Production of Amyloid Disease and Chronic Nephritis in Rabbits by Repeated Intravenous Injections of Living Colon Bacilli.—There is a considerable number of experiments on record in which amyloid has been induced in animals. For its production, bacteria of various kinds

as well as chemical substances were made use of. The positive results have been most frequently obtained in rabbits, but successful experiments have also been obtained in dogs, horses, fowl, and mice. BAILEY (*Jour. Exper. Med.*, 1916, xxii, 773) found amyloid degeneration in various organs of rabbits during an experimental study of the production of chronic nephritis by B. coli. Living cultures were injected every two to four days into rabbits. In a series of 15 animals positive results were obtained in 8. It was shown that time was an essential element, as no positive case was obtained under eighty-eight days, while every animal treated beyond this time showed amyloid. This product of tissue degeneration was not constant in its reaction to the various tests. It was found that whereas a positive result was obtained with methyl-violet or gentian violet, the iodin-sulphuric acid test was negative or indefinite. This lack in uniformity of the tests has been observed by others studying human material. The presence of amyloid was most commonly observed in the spleen, next the kidney, and finally the liver. As, in this series of experiments, suppuration was not induced in the tissues, it is evident that amyloid, though dependent upon the presence of bacterial growth, need not be associated with pus. The presence of amyloid in the kidney was associated with a subacute and chronic glomerulitis, parenchymatous degeneration, and some interstitial infiltration by round cells. Casts were present in tubules and a moderate fatty degeneration affected the convoluted tubules. The fatty deposit was not observed in association with the amyloid. No definite origin was determined for the amyloid deposit, but the author believed that it was of the nature of an infiltration rather than a production by either fibroblasts or endothelial cells.

Hematogenous Aortitis with Multiple Aneurysms.—Much the greater evidence upon the infection of arteries has been offered by French authors. This is more particularly true of infective arteritis associated with rheumatism. As early as 1840 Bouilland drew attention to the lesions in the heart and arteries as constituting an important phase in this disease. Brault, Stokes, Charcot, Vulpian, Corvisart, and others have described cases in which a more or less intense inflammation of the arterial walls was recognized and in some of which aneurysms had developed. Since 1900 at least 15 different French authors have reported cases and commented upon the presence of aneurysm associated with acute rheumatic fever. The majority of these cases were in young individuals ranging in age from three to twenty years. SOPRANA and PIAZZA (*Arch. de méd. exper.*, 1916, xxvii, 55) reported a case with multiple aneurysms of the aorta associated with rheumatism. The patient was a girl, aged twenty-one years, who had never had a previous attack of rheumatism. The fatal attack began suddenly and very acutely. She died within a month after the onset. During her illness she suffered from severe pain and swelling of the joints accompanied by fever. She also had much intrathoracic oppression with dyspnea. She died suddenly. At autopsy three aneurysms were found in the aorta, one of which had quite healthy looking walls and there was no evidence of damage upon the inner surface of the vessel. Microscopically the walls of each aneurysm showed much inflammatory infiltration as well as thickening of the adventitia. The media was much disturbed by the inflammatory processes with the destruction of

its essential elements, the muscle and elastic fibers. One aneurysm showed evidence of separation of the adventitia from the media thus forming a type of dissecting aneurysm. In this case the authors were unable to observe any evidence of organic syphilis and the Wassermann reaction was negative. They especially point out the fact that this patient had suffered her first attack of rheumatism during which the aneurysms had developed. They did not determine the nature of the microörganism which had led to tissue destruction. The aortic valves had been the seat of inflammatory reaction, but the infection associated with the aneurysm did not proceed directly along the aortic intima from the diseased valves. The authors believe that the infection of the aortic tissues had occurred by the carriage of the microörganisms to the adventitia. This is the more common mode of infection for these aortic lesions. The aneurysms develop only after the infection and its inflammation have brought about a certain amount of dissolution of the aortic wall.

Progressive Lenticular Degeneration.—New cases of Wilson's disease are periodically appearing in literature. As these cases are reported, the outstanding features of the disease are emphasized. Up to the present no one has analyzed the pathological findings to correlate them with the clinical picture. The constant presence of cirrhosis of the liver with degeneration of the nucleus lentiformis has not received adequate explanation. FARNELL and HARRINGTON (*Jour. Lab. and Clin. Med.*, 1916, 1, 561) have added another case to this interesting group. The patient was a girl of nineteen years who for four years had epileptoid seizures in which incoördination of the muscles of the extremities was one of the marked features. Her gait was somewhat spastic and at times her posture was fixed. Her mental development was below normal. At autopsy the striking finding was a marked cirrhosis of the liver of the portal type and the loss of the characteristic markings of the corpus striatum on the left side. The left caudate nucleus was smaller than normal and there was some dilatation of the left ventricle. The degeneration in the region of the nucleus lentiformis gave an appearance as if the various structures of this part were confluent. Small areas of necrosis were also present in this region. The microscopic examination of the affected brain tissues showed an increase of the glial tissue. The evidence of this degeneration was much more marked on the left than on the right side. There was no disturbance of the motor cortex or the cells of the anterior horns. The vessels were not sclerosed. The entire reaction appeared to be one of replacement gliosis which had not gone on to complete disintegration with cavity formation.

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